#12

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

NOV 14 2001

David T. Read
Acting Director Health Assessment Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

Dear Mr. Read:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 4,663,318. The application was filed on April 24, 2001, under 35 U.S.C. § 156.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term restoration. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)872-9411 (facsimile).

Karin Tyson
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: John Richards, Esq.
Ladas & Parry
26 West 61st Street
New York, NY 10023

RE: Reminyl

Docket No. 01E-0364

kt

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Re: Reminyl
Docket No.: 01E-0364

JAN 29 2002

The Honorable Q. Todd Dickinson
Director of U.S. Patent and Trademark Office
Commissioner for Patents
Box Pat. Ext.
Washington, D.C. 20231

Dear Director Dickinson:

This is in regard to the application for patent term extension for U.S. Patent No. 4,663,318, filed by Janssen Research Foundation, under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for Reminyl, the human drug product claimed by the patent.

The total length of the regulatory review period for Reminyl is 1,608 days. Of this time, 1,089 days occurred during the testing phase and 519 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: October 6, 1996.

   The applicant claims October 4, 1996, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was October 6, 1996, which was thirty days after FDA receipt of the IND.

2. The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act: September 29, 1999.

   FDA has verified the applicant's claim that the new drug application (NDA) for Reminyl (NDA 21-169) was initially submitted on September 29, 1999.

3. The date the application was approved: February 28, 2001.

   FDA has verified the applicant's claim that NDA 21-169 was approved on February 28, 2001.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: John Richards, Esq.
Ladas & Pary
26 West 61st St.
New York, NY 10023

#14

human drug product under section 505(b) of the act: June 9, 1997. FDA has verified the applicant's claim that the new drug application (NDA) for EVISTA (NDA 20–815) was initially submitted on June 9, 1997.

3. *The date the application was approved*: December 9, 1997. FDA has verified the applicant's claim that NDA 20-815 was approved on December 9, 1997.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,103 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (address above) written or electronic comments and ask for a redetermination by April 29, 2002. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by August 27, 2002. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (address above). Three copies of any information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 24, 2002.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 02–4682 Filed 2–27–02; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01E–0364]

Determination of Regulatory Review Period for Purposes of Patent Extension; REMINYL

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for REMINYL and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent that claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*.

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Office of Regulatory Policy (HFD–007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5645.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product REMINYL (galatamine hydrobromide). REMINYL is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for REMINYL (U.S. Patent No. 4,663,318) from Janssen Research Foundation, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated October 2, 2001, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of REMINYL represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for REMINYL is 1,608 days. Of this time, 1,089 days occurred during the testing phase of the regulatory review period, while 519 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) became effective:* October 6, 1996. The applicant claims October 4, 1996, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was October 6, 1996, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the act:* September 29, 1999. FDA has verified the applicant's claim that the new drug application (NDA) for REMINYL (NDA 21–169) was initially submitted on September 29, 1999.

3. *The date the application was approved:* February 28, 2001. FDA has verified the applicant's claim that NDA 21–169 was approved on February 28, 2001.

This determination of the regulatory review period establishes the maximum

potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,063 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (address above) written or electronic comments and ask for a redetermination by April 29, 2002. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by August 27, 2002. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch. Three copies of any information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 23, 2002.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 02–4683 Filed 2–27–02; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01E–0362]

Determination of Regulatory Review Period for Purposes of Patent Extension; TRAVATAN

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for TRAVATAN and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Office of Regulatory Policy (HFD–007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5645.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product TRAVATAN (travoprost). TRAVATAN is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another IOP lowering medication.

Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for TRAVATAN (U.S. Patent No. 5,889,052) from Alcon Laboratories, Inc., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated October 2, 2001, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of TRAVATAN represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for TRAVATAN is 1,694 days. Of this time, 1,441 days occurred during the testing phase of the regulatory review period, while 253 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) became effective:* July 28, 1996. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on July 28, 1996.

2. *The date the application was initially submitted with respect to the human drug product under section 505 of the act:* July 7, 2000. FDA has verified the applicant's claim that the new drug application (NDA) for TRAVATAN (NDA 21–257) was initially submitted on July 7, 2000.

3. *The date the application was approved:* March 16, 2001. FDA has verified the applicant's claim that NDA 21–257 was approved on March 16, 2001.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 484 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (address above) written or electronic comments and ask for a redetermination by April 29, 2002. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Re: Reminyl
Docket No. 01E-0364

The Honorable James. E. Rogan
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Box Pat. Ext.
P.O. Box 2327
Arlington, VA 22202

DEC 10 2002

Dear Director Rogan:

This is in regard to the patent term extension application for U.S. Patent No. 4,663,318 filed by Janssen Research Foundation under 35 U.S.C. § 156. The patent claims the human drug product Reminyl (galatamine hydrobromide), new drug application NDA 21-169.

In the February 28, 2002, issue of the Federal Register (67 Fed. Reg. 9301), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before August 27, 2002, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: John Richards, Esq.
Ladas & Pary
26 West 61th St.
New York, NY 10023

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

#16

John Richards, Esq.
Ladas & Parry
26 West 61st Street
New York, NY 10023

In Re: Patent Term Extension
Application for
U.S. Patent No. 4,663,318

MAILED

JAN 16 2004

REEXAM UNIT

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 4,663,318, which claims the human drug product REMINYL® (galantamine hydrobromide), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 1,064 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 1,064 days.

The period of extension has been calculated using the Food and Drug Administration (FDA) determination of the length of the regulatory review period published in the Federal Register of February 28, 2002 (67 Fed. Reg. 9301). Under 35 U.S.C. § 156(c):

Period of Extension = ½ (Testing Phase) + Approval Phase
= ½ (1,089) + 519
= 1,064 days

Since the regulatory review period began October 6, 1996, after the patent issue date (May 5, 1987), the entire period has been considered in the above determination. No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

Neither the limitations of 35 U.S.C. § 156(g)(6) nor the 14 year limitation of 35 U.S.C. § 156(c)(3) operate to reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.	:	4,663,318.
Granted	:	May 5, 1987
Original Expiration Date	:	January 15, 2006

Applicant	:	Bonnie Davis
Owner of Record	:	Synaptech, Inc.
Title	:	Method of Treating Alzheimer's Disease
Classification	:	514/215
Product Trade Name	:	REMINYL® (galantamine hydrobromide)
Term Extended	:	1,064 days
Expiration Date of Extension	:	December 14, 2008

Any correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450 Alexandria, VA 22313-1450

By FAX: (703) 872-9411

Telephone inquiries related to this determination should be directed to the undersigned at (703) 306-3159.

Karin Ferriter
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: David T. Read
Acting Director Health Assessment Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

RE: REMINYL® (galantamine hydrobromide)
FDA Docket No.: 01E-0364

#.7

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1st Resp.

In re application of: BONNIE DAVIS

Serial No.: 06/819,141 (U.S. PATENT 4,663, 318) Group No.: 1205

Filed: JANUARY 15, 1986 Examiner: FRIEDMAN. STANLEY

For:

Attorney Docket No.: U 5631 (NPSP 040620)

MAIL STOP RECONSTRUCTION
COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

RESPONSE

This is in response to the Office Action with date of mailing February 4, 2004 setting a six month response deadline.

CERTIFICATE OF MAILING/TRANSMISSION (37 CFR 1.8a)

I hereby certify that this correspondence is, on the date shown below, being:

MAILING

☒ deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to MAIL STOP RECONSTRUCTION, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450

FACSIMILE

☐ transmitted by facsimile to the Patent and Trademark Office

Signature Hugh Wotherspoon

Hugh Wotherspoon
(type or print name of person certifying)

Date: May 27, 2004

EV 416 707 865 US

The file opened by Ladas & Parry for USSN 819,141 filed January 15, 1986 was destroyed. We are uncertain when, but to the best of my knowledge this was prior to June 1995. Subsequent to the destruction of our file we obtained from the United States Patent Office a copy of the USPTO file wrapper. From the information we have available it appears that this was ordered in June 1995. A copy of this copy of the file wrapper is enclosed together with a list of documents we are providing. Since our file has been destroyed we are not aware of any additional correspondence between the office and the patentee which we are not providing. Since the copy documents obtained from the USPTO did not include copies of the documents submitted with our December 15, 1986 letter to the USPTO mentioned in the file wrapper we subsequently ordered these from the Washington DC search firm of Allbright and Associates (who in turn obtained them from the NIH) and these are also listed on the list.

Please acknowledge receipt of this communication by date stamping and returning the attached post card.

Respectfully submitted,

JOHN RICHARDS
c/o Ladas & Parry
26 West 61st Street
New York, N.Y. 10023
Telephone No.(212) 708-1915
Registration No. 31053

USSN 06/819141

LIST OF ALL OF THE CORRESPONDENCE BETWEEN THE PATENTEE AND THE USPTO FOR THE ABOVE APPLICATION

ITEM	PARTIES	DATE	NUMBER OF SHEETS
Contents Sheet (U.S. Govt Printing Office 1981-349-868)		Marked 'Received March 4, 1986'.	1
New Application Transmittal (Under Divider 1)	Commissioner of Patents and Trademarks and John Richards	January 15, 1986	5
Patent and Trademark Office Fee Record Sheet (Under Divider 1)			1
Patent Specification (Under Divider 1)			6
Combined Declaration and Power of Attorney (Under Divider 1)	Dr Bonnie Davis	December 26, 1985	3
Verified Statement Claiming Small Entity Status (Under Divider 1)	Dr Bonnie Davis	December 26, 1985	2
Patent and Trademark Office Form PTO 436L			2
Form PTOL -85b; Issue Fee Transmittal	John Richards	Illegible	1
Form PTOL -85c; Issue Fee Transmittal	John Richards	Jan 15 '87	1
Certificate of Mailing of Issue Fee	John Richards	January 15, 1987	1
Statement that 'This paper was found to be missing...etc' (Under Divider 6)		Undated	1
Form PTOL-37; Notice of Allowability (Under Divider 5)	Stanley J Friedman		1

ITEM	PARTIES	DATE	NUMBER OF SHEETS
Form PTO-892; Notice of References Cited (Under Divider 5)	Friedman	9/26/86	1
Form PTOL-85; Notice of Allowance and Issue Fee Due (Under Divider 5)	Friedman S and Lester Horwitz	Mailed 10/20/86	1
Letter (Under Divider 5)	John Richards and Commissioner of Patents and Trademarks	December 15, 1986	6
Amendment Responsive to Office Action of April 10, 1986 (Under Divider 4)	John Richards (by Joseph H. Handelman) and Commissioner of Patents and Trademarks	September 9, 1986	9
Journal of the Highest Nervous Activity, Vol XXIV 1974 Issue 1; 'Interrelation Between the Ventral and Dorsal Hippocampus at Improvement and Deterioration of the Short Term Memory', V.A. Kraus. (Under Divider 4)			25
Journal of the Highest Nervous Activity, Vol XXIV 1976 Issue 5; 'The Action of Cholinergic Drugs in Experimental Amnesia'; S. R. Chaplygina and R. Yu. Ilyuchenok (Under Divider 4)			10
Examiner's Action (PTOL-326) (Paper Number 2) (Under Divider 3)	Commissioner of Patents and Trademarks and Lester Horwitz c/o Ladas & Parry	Mailed 4/10/86	3
Form PTO -892 (Attachment to Paper Number 2) (Under Divider 3)			1

ITEM	PARTIES	DATE	NUMBER OF SHEETS
Petition and Fee for Extension of Time (Under Divider 2)	John Richards (by Joseph H. Handelman) and Commissioner of Patents and Trademarks	September 9, 1986	2
The following references are the references obtained from Allbright and Associates as mentioned in our Response.			
'Acta anaesth. scand. 1980, 24, 166-168' (D. Cozanitis et al)			
'Physiology and Behavior, Vol 14, pp 563-566....' (H Rigter et al)			
'Physiology and Behavior, Vol 13, pp 381-388..' (H Rigter et al)			
'COMMUNICATIONS, J. Pharm. Pharmac., 1977, 29, 110.' (H Rigter et al)			
'The Neuropeptides; Pharmacology Biochemistry and Behavior, Vol 5, Suppl. 1, pp 41-51...' (James F Flood et al)			
'Pharmacology Biochemistry & Behavior, Vol 4, pp. 703-707' (Marie E. Gibbs)			
'Pharmacology Biochemistry and Behavior, Vol 2, pp. 663-668...' (Lyle H. Miller et al)			
'Journal of the american geriatrics society Vol XXV, January 1977, Number 1, pp 1-19' (Adrian Ostfield et al)			

ITEM	PARTIES	DATE	NUMBER OF SHEETS
'The Journal of Nervous and Mental Disease...; Vol 163, No 1. pp 59-60' (Peter Sheldrake et al)			
'Journal of Comparative and Physiological Psychology 1976, Vol 90, No. 11, 1082-1091' (James M. Murphy et al)			
'Acta Physiologica et Pharmacologica Bulgarica, Vol 2, No. 2 Sofia 1976 pp 49-57' (K. Roussinov et al)			
'Arneim-Forsch. (Drug Res) 26, Nr 10a (1976) pp 1947-1950' (D. Hadjiev et al)			
'Current Medical Research and Opinion; Vol 4, No. 4, 1976 pp 303-306' (B. W. Hackman et al)			
'Journal of Medical Chemistry; Vol 29, Number 7, July 1986 pp 1125-1130' (Fred M. Hershenson et al)			
'Neurobiology of Aging, Vol 6, pp 95-100, 1985' (Cecilia A. Peabody et al)			
JAMA, Nov 21, 1977-Vol 238, No. 21 pp 2293-2294' (Anis Baraka et al)			
'Journal of Clinical and Hospital Pharmacy (1985) 10, 327-336' (M.J.. Kendall et al)			
'Indian J Pediat; 32 : 89, 1965' Notes			
Pharmacology Biochemistry and Behavior, Vol. 2, pp. 557-561' (Bill E. Beckwith et al)			

ITEM	PARTIES	DATE	NUMBER OF SHEETS
Pharmacology Biochemistry & Behavior, Vol. 4, pp 123-127' (Tibor Palfai et al)			
'Acta Physiologica et Pharmacologica Bulgarica, Vol 2, No. 3 Sofia-1976 pp 66-71' (K Roussinov et al)			
' Journal of the american geriatrics society Vol XXV, July 1977, Number 7, pp 289-298' (Meyer et al)			

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

2nd Reis.

In re application of: BONNIE DAVIS

Serial No.: 06/819,141 (U.S. PATENT 4,663, 318) Art Unit.: 1205

Filed: JANUARY 15, 1986 Examiner: FRIEDMAN. STANLEY

For:

Attorney Docket No.: U 5631 (NPSP 040620)

MAIL STOP RECONSTRUCTION
ATTN: RUTH BLAKENEY
200 12TH STREET SOUTH
GATEWAY 4 BUILDING
4TH FLOOR
ALEXANDRIA, VIRGINIA 22202

RESPONSE

I refer to the telephone discussion between Ms. Blakeney and Hugh Wotherspoon on September 21, 2004.

As agreed, I enclose a full copy of our May 27, 2004 response in these reconstruction proceedings including a copy of the postcard stamped as received by the Patent and Trademark Office on June 1, 2004.

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☐ deposited with the United States Postal Service in an envelope addressed to Mail Stop Reconstruction, ATTN: Ruth Blakeney at the Gateway 4 Building, Alexandria, VA 22202

37 C.F.R. 1.8(a)

☐ with sufficient postage as first class mail.

37 C.F.R. 1.10*

☒ as "Express Mail Post Office to Address" Mailing Label No. EV 481670865 US (mandatory)

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office, to **(703) 872-9306**

Date: October 7, 2004

Signature

Janie Jurica

(type or print name of person certifying)

***WARNING:** *Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

EV 481670865 US

Please update the "PAIR" system to record the receipt of the original response by the Patent Office on June 1, 2004.

Please also expedite the reconstruction of your file for this patent.

We anxiously await the issuance of a Certificate of Patent Term Extension for this patent and we do not wish the file reconstruction proceedings to delay the issuance of the certificate.

Please acknowledge receipt of this communication by date stamping and returning the attached post card.

Respectfully submitted,

John Richards
c/o Ladas & Parry
26 West 61st Street
New York, New York 10023
Telephone No. (212) 708-1915
Registration No. 31053

UNITED STATES PATENT AND TRADEMARK OFFICE

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OCT 22 2004

John Richards, Esq.
Ladas & Parry
26 West 61st Street
New York, NY 10023

In Re: Patent Term Extension
Application for
U.S. Patent No. 4,663,318

Dear Mr. Richards:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 4,663,318 for a period of 1,064 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Telephone inquiries regarding this communication should be directed to the undersigned by telephone at (571)272-7744, or at Karin.Ferriter@uspto.gov by e-mail.

Karin Ferriter
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
HFD - 13
5600 Fishers Lane
Rockville, MD 20857

Attention: Claudia Grillo

RE: REMINYL® (galantamine hydrobromide)
FDA Docket No.: 01E-0364

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	4,663,318
(45)	ISSUED	:	May 5, 1987
(75)	INVENTOR	:	Bonnie Davis
(73)	PATENT OWNER	:	Synaptech, Inc.
(95)	PRODUCT	:	REMINYL® (galantamine hydrobromide)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 4,663,318 based upon the regulatory review of the product REMINYL® (galantamine hydrobromide) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,064 days

from January 15, 2006, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the United States Patent and Trademark Office to be affixed this 16th day of September 2004.

Jon W. Dudas

Jon W. Dudas
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

EXHIBIT 3

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bonnie Davis

Serial No.: 819,141 Group No.: 125

Filed: January 15, 1986 Examiner: Friedman

METHOD OF TREATING ALZHEIMER'S DISEASE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

SIR:

AMENDMENT RESPONSIVE TO OFFICE ACTION OF APRIL 10, 1986

Please amend the application as follows:

IN THE SPECIFICATION

At page 1, line 12, change "anesth. scand." to read -- Anesth. Scand.--.

Page 2, line 29, change "from" to read --form--.

Page 2, line 33, correct spelling of --aids--.

IN THE CLAIMS

Claim 1, line 1, delete "and diagnosing".

R E M A R K S

The application is amended to meet the Examiner's rejection under 35 USC 112 by deletion of reference to diagnosis. This amendment is made without prejudice to the possibility of filing a divisional or continuation-in-part application directed to

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOSEPH H. HANDELMAN
(Type or print name of person mailing paper)

Date: SEPTEMBER 9, 1986

Joseph H. Handelman
(Signature of person mailing paper)

diagnosis in due course.

The amendments to the specification correct obvious typographical errors.

Alzheimer's disease is a major and growing problem in our society (see the paper by Hershenson & Moos in July 1986 Journal of Medical Chemistry submitted herewith). It is estimated that there are over 1,000,000 sufferers of this disease in the United States alone. Symptoms include depression, intellectual decline, memory loss, speech difficulties and muscular spasms. Little is known about the root cause of the condition and although useful results have been reported in some cases by treatment with physostigmine, its poor therapeutic index is likely to preclude its widespread use and there is no generally effective treatment available. As noted in an article by Kendall et al, submitted herewith, (J Clin Hos Pharmac (1985) 10 327-336), "The theoretical possibility of developing a long acting preparation of an agent with good brain penetration and possibly some selectivity of action towards the relevant cortical cholinergic system, must be seen as a major challenge for researchers working on Alzheimer's disease". Applicant currently has experiments underway using animal models which are expected to show that treatment with galanthamine does result in an improvement in the condition of those suffering from Alzheimer's disease. It is expected that data from this experimental work will be available in two to three months and will be submitted to the Examiner promptly thereafter. Furthermore, galanthamine is currently being used in Europe to assist in post-operative recovery from anaesthesia and so is unlikely to suffer the problems of possible toxicity encountered with physostigmine (Acta Anesth Scand (1980) 21:166).

The rejections under 35 USC 103 are respectfully

traversed. The rejection is based on two Chemical Abstract references noted in the specification. The first, by Kraus, is an abstract of a paper published in the Journal of Highest Nervous Activity Volume 24 (1974). The second is an article by Chaplygina and Ilyuchenok. Applicant has had translations of each of the original papers prepared and these are submitted herewith.

The Kraus article related to an investigation of the effects of various chemicals on short-term memory and the activity of the hippocampus in normal dogs. It concluded that the effect of galanthamine was about the same as that of strychnine and lower than that of phenamine and ethimizol.

The Chaplygina article describes work done on restoration of conditioned reflexes after memory in mice had been destroyed, for example, by electro-shock.

The Examiner's comment on this art, namely that it "teaches activities for the instant agent that would have value in treating the effects of Alzheimer's disease" is not entirely clear. However, apparently what the Examiner means is that since these articles indicate that galanthamine has an effect on improving short-term memory and on restoring memory after it has been destroyed, it would be useful in treating Alzheimer's disease. This is a non sequitur.

The mechanism of memory and indeed many brain functions are still only hazily understood at best. One cannot predict with any degree of confidence what the effect of any given chemical on a particular brain function or brain condition may be. While it is true that studies have shown that impairment of memory may result from certain specific factors varying from brain damage, though diminution of blood flow as a result of arteriosclerosis in brain arteries to chemical effects such as

thiamine deficiency in causing Wernicke-Korsakoff syndrome, the cause of "normal" establishment of memory and forgetfulness is still not understood. It is true that in Alzheimer's disease, there is memory loss. However, this is apparently associated with physiological changes in the brain including degeneration of nerve cells in the frontal and temporal lobes, damage in the neural pathways to the hippocampus and the creation of neurofibrillary tangles in nerve cells. There is no way of predicting that because a chemical may have an effect on memory in a normal brain (which is what is indicated in the cited references) it would have any effect on a brain that has suffered such physiological changes. To say that simply because a particular drug has some effect on a symptom caused by one underlying condition, it will have a useful effect on another underlying condition is clearly wrong. To predict that galanthamine would be useful in treating Alzheimer's disease just because it has been reported to have an effect on memory in circumstances having no relevance to Alzheimer's disease would be as baseless as predicting that one should treat impaired eyesight due to diabetes with drugs effective in ameliorating impaired vision due to other causes such as glaucoma. In fact, since the animals used in the studies of Kraus and Chaplygina were normal, an even more pertinent analogy can be made. The prediction that galanthamine would be useful to treat Alzheimer's disease because it is known to have an effect on memory in normal animals is as baseless as a prediction that impaired eyesight due to diabetes would respond to devices (eyeglasses) or treatments (eye exercises) known to improve the vision of normal persons. In diabetes, impaired eyesight is most often the result of bleeding from the retina and would not be improved by eyeglasses or such treatments.

In fact, the art cited in the present case does not even provide the basis for speculation at this level. Turning first to the Kraus article, the learning task utilized in this study is poorly described, but seems to be the effect of a delay between the presentation of a stimulus and the time in which a nondiseased dog is allowed to make its conditioned response. The Alzheimer's patient suffers from problems in language, praxis, naming, and the ability to learn new information. It is the constellation of these abnormalities that gives the Alzheimer's patient a pattern of dementia that is being regarded as relatively diagnostic. Thus, improving a small aspect of memory function in a nondiseased dog whose brain has neither the anatomical nor biochemical lesions of Alzheimer's disease is far from a valid test of a medication for Alzheimer's disease. It is not surprising that positive results from the experiments performed by Kraus are found for a class of compounds (amphetamine like) that are ineffective in Alzheimer's disease. Recently models have been established with animals with selective neurotransmitter and anatomic deficits that mimic Alzheimer's disease, that have some validity, and could be anticipated to have predictive ability. Such is not the case for this conditioned learning paradigm applied to intact animals.

Apart from galanthamine, three drugs (ethimazol, phenamine and strychnine) are referred to by Kraus as being useful in their effects on short-term memory. Ethimazol acts by increasing cAMP, a major effect of methamphetamine as well (Biull Exp Biol Med (1977) 83:185). Phenamine is methamphetamine. Methamphetamine has been directly tested in patients with Alzheimer's dementia; it has absolutely no effect (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1). Strychnine is a convulsant which stimulates brain non-

specifically (Gilman AG, Goodman LS, Rall TW, Murad F, eds., The Pharmacological Basis of Therapeutics, Macmillan Publ. Co., New York, 1985, p. 582). Pentylenetetrazol (Metrazol), a compound with convulsant and stimulant properties analogous to those of strychnine, does not improve cognitive function in Alzheimer's patients (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177). Thus, the ability of a drug to enhance memory in the experiments performed by Kraus does not indicate that the drug will be of use in Alzheimer's disease.

The teaching of the Chaplygina article does not take matters any further forward. It teaches that galanthamine reverses the amnesia-producing effects of scopolamine. However, this would be expected of an anticholinesterase. Nothing in this teaching leads to an expectation of utility against Alzheimer's disease. There are many anticholinesterase drugs available but Alzheimer's disease is still regarded as being effectively untreatable.

Applicant carried out a survey of drugs which were reported in the literature to have been useful in enhancing short-term memory over the period 1973-1976 and followed this up with a survey of whether any of them has subsequently been reported as having been tried in connection with Alzheimer's disease. The results are as follows:

39 compounds were reported to facilitate memory in various studies of animals and humans without brain lesions: adrenocorticotrophic hormone (Behav Biol (1976) 16:387, J Pharm Pharmac (1977) 29:110), ACTH 4-10 (J Pharm Pharmac (1977) 29:110, Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41, Physiol Behav (1975) 14:563, Pharmacol Biochem Behav (1974) 2:663, Physiol

Behav (1974) 13:381, Sachar EJ, ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), adenosine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), amphetamine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory MIT Press, Cambridge, Mass., 1976, p.483 Pharmacol Biochem Behav (1976) 4:703, Pharmacol Biochem Behav (1974) 2:557, Behav Biol (1977) 20:168), apovincaminate (Arzneim-Forsch (1976) 26:1947), caffeine (Acta Physiol Pharmacol Bulg (1976)2:66), desglycine lysine vasopressin (Sachar EJ, ed, Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), echinopsin (Acta Physiol Pharmacol Bulg (1976) 2:66), fluorothyl (Physiol Behav (1975) 14:151), glutamate (Brain Res (1974) 81:455), heavy water (Naturwissenschaften (1974) 61:399), histamine (Acta Physiol Pharmacol Bulg (1976) 2:49), imidazole (Acta Physiol Pharmacol Bulg (1976) 2:49), imipramine (Pharmacol Biochem Behav (1974) 2:663), isoprenaline (Pharmacol Biochem Behav (1976) 4:703), ß-lipotropin (Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41), magnesium pemoline (Behav Biol (1975) 15:245), -melanocyte stimulating hormone (J Pharm Pharmacol (1977) 29:110), methoximine (Pharmacol Biochem Behav (1976) 4:703), norepinephrine (Pharmacol Biochem Behav (1976) - 4:703, Brain Res (1975) 84:329), orotic acid (Arch Int Pharmacodyn (1974) 211:123), papaverine (Acta Physiol Pharmacol Bulg (1976) 2:49), parachlorophenylalanine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), pargyline and pheniprazine (monoamine oxidase inhibitors, (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), pentylenetetrazol (Pharmacol Biochem Behav (1976) 4:123), physostigmine (Rosenzweig

MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), picrotoxin (Behav Biol (1977) 20:168), piperazine estrone sulfate (Curr Med Res Opin (1976) 4:303), piracetam (Psychopharmacology (1976) 49:307), progestagens (J Nerv Ment Dis (1976) 163:59), strychnine (Behav Biol (1977) 20:168, Arch Int Pharmacodyn (1974) 211:123), thyrotropin-releasing hormone (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), thyroxine (J Comp Physiol Psychol (1976) 90:1082), tranylcypromine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), uridine monosphate (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), and vasopressin (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1).

Applicant has found that of these the literature reports that ten have been tested for treatment of Alzheimer's disease. These were ACTH 4-10 (J Clin Hosp Pharmac (1985) 10:327, Neurology (1985) 35:1348), apovincaminate (J Clin Hosp Pharmac (1985) 10:327), magnesium pemoline (Lipton MA, DiMascio A, Killam KF, eds., Psychopharmacology: A Generation of Progress, Raven Press, New York, 1978, p. 1525), methylphenidate (amphetamine modified to reduce peripheral side effects (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1), monoamine oxidase inhibitors (J Am Geriat Soc 1977 25:1), papaverine (J Clin Hosp Pharmac (1985) 10:327), pentylenetetrazol (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177.), piracetam (J Clin Hosp Pharmac (1985) 10:327, Am J

Psychiat 1981 138:593), tyrosine (increases norepinephrine, J Am Geriat Soc (1977) 25:289), vasopressin (J Clin Hosp Pharmac (1985) 10:327, J Am Geriat Soc (1977) 25:289, Neurobiology of Aging (1985) 6:95) and physostigmine as discussed above.

With the exception of physostigmine, none of these was reported to be effective in treating Alzheimer's disease.

As shown from the literature references submitted with the response, the effective treatment of Alzheimer's disease has proved to be very difficult. Many approaches have been tried. None has been successful. Galanthamine and its properties have been known for many years. No one has previously suggested that it should be used to treat Alzheimer's disease. Many drugs having similar properties to galanthamine have been tried unsuccessfully. Under these circumstances, it is quite clear that it could not possibly be obvious to one skilled in the art to use galanthamine to treat Alzheimer's disease.

In view of the foregoing, reconsideration of the 35 USC 103 rejection is respectfully requested.

Respectfully submitted,

John Richards by
Joseph H. Handelman
REG. NO. 26179

JOHN RICHARDS
c/o LADAS & PARRY
26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

EXHIBIT 4

P.O. Box 4000
Princeton, NJ 08543-4000
(609) 921-4610
Telex: 843334 SQUIBB PRIN
Rapifax: (609) 921-5360

Gary A. King, Ph.D.
Scientific Director
Worldwide Licensing and Business Analysis

E.R. Squibb & Sons

December 21, 1989

Dr. Bonnie Davis
17 Sea Crest Drive
Huntington, New York 11743

Dear Dr. Davis:

Scientists in our CNS research group have now completed their evaluation of data on galanthamine and its analogues, and, therefore, I am writing to convey the results of that evaluation. The consensus of opinion is that Bristol-Myers Squibb should not seek a license to these compounds at the present time. Our decision is based upon concerns for the clinical and commercial success of galanthamine, and the very early stage of development, and corresponding lack of data for the analogs.

The very narrow therapeutic window that was observed in animal studies with galathamine was considered to be a significant shortcoming. Impairment of response acquisition is normal mice, at doses that were not different than the dose that reversed behavioral deficits in lesioned animals, also caused concerns for the therapeutic ratio in man. The occurrence of salivation in monkeys at therapeutic doses of galathamine, also raised similar concerns.

Unfortunately, clinical experience with galathamine in Alzheimer's patients is, presently, very limited. Therefore, the therapeutic benefit and long term safety and tolerability of galanthamine is still a matter for speculation.

As we have discussed previously, the fact that galanthamine is protected only by use patents, and that marketing exclusivity might only be a certainty in the U.S., means that galathamine will be of less interest to us than a similar drug protected by composition of matter patents in all major countries.

As a corollary to the above, novel galathamine analogs could be of greater interest, if more extensive animal testing reveals that these drugs have a broad therapeutic window and a large safety ratio. Therefore, provided that you are still free to discuss these compounds, we may be interested in reviewing the results of future studies.

I regret that we cannot pursue your proposal further at the present time. However, I appreciate very much the earnest cooperation that you have given us, and I wish you continuted success.

Sincerely yours,

Gary King

Gary A. King

cc: D. Temple
J. Vida

Plaintiff's Exhibit
PX - 119

EXHIBIT 5

Dr. D. Cozanitis
University Helsinki
Central Hospital
Department of Anesthesia SF-00290
Helsinki 29, Finland

Dear Dr. Cozanitis,

I am interested in obtaining gulanthamine hydrobromide for use in the United States. Could you please send me the name and address of the manufacturer so that I may get the information required by our government regulatory agencies?

Thank you for your help, and congratulations on your fine work.

Very truly yours,

BONNIE M. DAVIS, M.D.
Medical Director, Special Treatment Unit, Bronx VA Medical Center
Assistant Professor of Psychiatry
Mount Sinai School of Medicine

Plaintiff's Exhibit
PX - 121

EXHIBIT 6

Department of Anaesthesia
Helsinki University Central Hospital
SF-00290 Helsinki 29, Finland
8th October, 1980.

Dr. Bonnie M. Davis, M.D.
Medical Director
Special Treatment Unit
Bronx VA Medical Center
130 West Kingsbridge Road
Bronx, NY 10468, USA.

Dear Dr. Davis,

Thank you for your letter concerning galanthamine hydrobromide. I suggest you write to: Eng. St. Jordanov
Chief of Department, "Registration and Patents"
P H A R M A C H I M
16, Iliensko Chaussee
Sofia, Bulgaria
telling him that I have advised your writing him.

Unfortunately, the process of getting galanthamine has been a slow one, so you might follow-up your letter with a cable or telex:

Cable address: PHARMACHIM, SOFIA

Telex: 22597.

I hope this information will be of benefit to you and if I can be of more help, please do not hesitate to write me. With best wishes, I am

Very sincerely,

D. A. Cozanitis

Demitri A. Cozanitis
BScPharm., MBChB, MD, DTM&H

Plaintiff's Exhibit
PX - 122

EXHIBIT 7

March 16, 1983

526/116A

Dr. Eng. St. Jordanov
Chief, Department of Registration and
Patents
PHARMACHIM
16, Iliensko Chaussee
Sofia, Bulgaria

Dear Dr. Eng. St. Jordanov:

I am an endocrinologist investigating cholinergic mechanisms of hormonal control. Dr. D.A. Cozanitis has published interesting investigations using your drug, galanthamine hydrobromide, and he has advised me to contact you.

I would sincerely appreciate information on how to purchase galanthamine from you for use in my research.

Thank you!

BONNIE M. DAVIS, M.D.
Medical Director, Special Treatment
Unit, Bronx VA Medical Center
Assistant Professor of Medicine and
Psychiatry, Mt. Sinai School of Medicine

Plaintiff's Exhibit
PX - 123

EXHIBIT 8

GALANTHAMINE: AN OLD CHOLINESTERASE INHIBITOR REVISITED

Domino, E.F.
Dept. of Pharmacology, University of Michigan, Ann Arbor, MI 48109

Galanthamine (4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro [3a,3,2-ef][2]benzazepin-6-ol is a tertiary amine reversible cholinesterase inhibitor originally isolated from Caucasian snowdrops, Galanthus woronowii Vel. A great deal of research has been devoted to its isolation, chemical synthesis and pharmacology in the 1950s through the 1980s in Bulgaria and other countries, especially in eastern Europe. It is available through Pharmachim in Bulgaria as galanthamine hydrobromide (Nivalin) for both parenteral as well as oral use. Our experimental supply in ampule form was obtained through the kindness of Prof. D.A. Kharkevich of the USSR. There are reports in the literature that galanthamine is longer acting than physostigmine, especially in man. Our own experience in rats trained on an FR4 bar pressing schedule is that it is
23 less potent on a mg/kg basis than physostigmine but of equal duration of action. Hence, we concluded, on the basis of this preliminary evidence in rats, that galanthamine has no advantage over physostigmine. Pharmacokinetic studies in rats indicate that its plasma concentrations over time fit a 2 compartment model with a $t_{1/2}$ of about 45 min following i.v. administration. Galanthamine has an oral bioavailability of about 65%. Further research is indicated because of the wide clinical experience in eastern European countries that galanthamine is a useful agent with minimal side effects for a variety of indications. To our knowledge, the drug has not been studied systematically in patients with Alzheimer's Disease. Galanthamine should be compared to physostigmine further in a large variety of species of animals including normal humans prior to a possible clinical trial in patients with Alzheimer's Disease.
(Supported in part by the Psychopharmacology Research Fund 361024.)

METHANESULFONYL FLUORIDE: A CNS SELECTIVE INHIBITOR OF ACETYLCHOLINESTERASE

Moss, D.E., Kobayashi, H., Pacheco, G., Palacios, R. and Perez, R.
University of Texas at El Paso: El Paso, Texas 79968

Methanesulfonyl fluoride (MSF) is an irreversible inhibitor of acetylcholinesterase that has the remarkable quality of being selective for the central nervous system. MSF can produce up to 90% inhibition of rat brain cholinesterase with less than 35% inhibition or peripheral enzyme measured in smooth muscle, skeletal muscle and heart. Experiments conducted in monkeys (M. fasicularis) have shown that a single injection of 1.5 mg/kg of MSF will produce over 85% inhibition of brain cholinesterase as measured by CSF samples. Enzyme activity returned to the CSF with a
24 half-time of 2.16 days. Monkeys treated with 1.5 mg/kg MSF for 12 injections given twice per week showed 80% inhibition of cortex enzyme as measured by cortical biopsies taken 2 or 3 days after the last injection. These data show that cortical enzyme is replaced more slowly than CSF enzyme and that very high levels of inhibition can be maintained in the cortex. At no time during treatment did any monkey show toxic effects as shown by blood chemistry, behavior, or loss of weight or vigor. Additional experiments have shown that MSF is selective for human cortex AChE (as compared to BChE) and that MSF is efficacious in reducing scopolamine-induced amnesia in rats in a Y-maze brightness discrimination tas

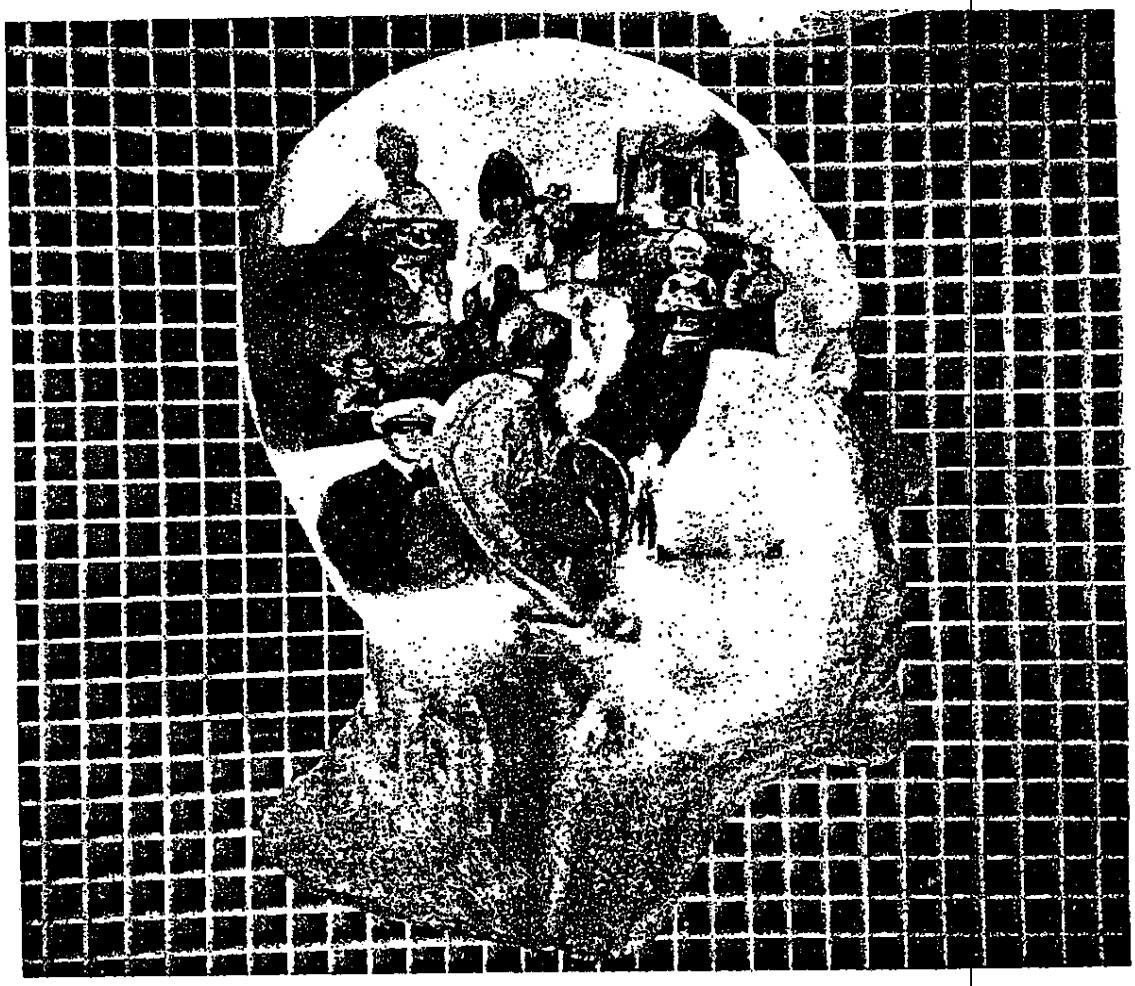
Because of the remarkably low toxicity associated wit
cholinesterase inhibition produced by MSF, it appears that M
and efficacious as a therapeutic agent in dementia of the Al
for an IND from the FDA for human trials is pe
Dallas, T

ADVANCES IN ALZHEIMER THERAPY: CHOLINESTERASE INHIBITORS

AN INTERNATIONAL SYMPOSIUM

Saturday and Sunday, March 19 and 20, 1988

Organized by
Southern Illinois University
School of Medicine
at
801 N. Rutledge
South Auditorium
Springfield, Illinois



Sponsored by:
The World Federation of Neurology Research Group on Dementias
and the Institute of Developmental Neuroscience and Aging

SUNDAY, March 20, 1988

New Approaches to Pharmacotherapy of Alzheimer's Disease
L. Ravizza, E. Domino (Chairmen)

7:30- 8:00	Breakfast and Registration
8:00- 8:20 (22)	Studies on the Nootropic Effects of Huperzine A and B: Two Selective AChE Inhibitors Tang, X.C. - Shanghai Institute of Materia Medica, Shanghai
8:20- 8:40 (23)	Galanthamine: An Old Cholinesterase Inhibitor Revisited Domino, E.F. - Department of Pharmacology, University of Michigan, Ann Arbor
8:40- 9:00 (24)	Methanesulfonyl Fluoride: A CNS Selective Inhibitor of Acetylcholinesterase Moss, D.E. - Department of Psychology, University of Texas at El Paso, El Paso
9:00- 9:20 (25)	Intra-Cerebro-Ventricular Bethanechol (ICVB) Read, S.L. - John Douglas French Center, Los Alamitos
9:20- 9:40 (26)	Intraventricular Bethanechol Infusion for Alzheimer's Disease Fox, J.H. - Rush Alzheimer's Disease Center, Chicago
9:40-10:00 (27)	Clinical Experience with R-86 and Oxotremorine Davidson, M. - Mt. Sinai Hospital, New York
10:00-10:30	Coffee Break/Posters
10:30-10:50 (28)	Neurochemical Changes in Lymphocytes of Patients with Alzheimer's Diseases Ravizza, L. - University of Turin Medical School, Turin
10:50-11:10	Clinical Neurochemical and Neurophysiological Comparison of Cholinergic Deficiencies in Alzheimer's and Parkinson's Disease Riekkinen, P. - University of Kuopio Medical School, Kuopio
11:10-12:00	General Discussion
12:15	CME Evaluation
12:30	Return to Hotel

EXHIBIT 9

MYLAN PHARMACEUTICALS INC.

April 13, 1990

Bonnie Davis, M.D.
SYNAPTEC, INC.
17 Seacrest Drive
Huntington, New York 11743

Dear Bonnie:

I have reviewed the research and development program for the galanthamine project with Mylan's Executive Committee and our New Product Development Team. Regretfully, we have elected to terminate further licensing discussions. We find this project is not consistent with our current research program and capabilities.

I appreciate the opportunity to have worked with you and I thank you for your interest in Mylan. I wish you every success with this project.

Very truly yours,

Cheryl Blume

Cheryl D. Blume, Ph.D.
Vice President,
Scientific Affairs

CDB/kg

Plaintiff's Exhibit
PX - 173

P. O. Box 4310 • 781 Chestnut Ridge Road • Morgantown, West Virginia 26505-4310 U.S.A. • (304) 599-2595 • FAX (304) 598-3232
FLORIDA OFFICE: 3820 Northdale Boulevard • Suite 300B • Tampa, Florida 33624 • (813) 960-9343 • Telecopier: (813) 968-7138

EXHIBIT 10

REFERENCES

1. Editorial. Dementia — the quiet epidemic. Brit. Med. J. 1978; 1: 1-2.
2. HOLLISTER, L.E. Drugs for mental disorders of old age. J.A.M.A. 1975; 234: 195-198.
3. SAKALIS, G., Oh., D., GERSHON, S. et al. A trial of Gerovital H-3 in depression during senility. Curr. Ther. Res. 1974; 16: 59-63.
4. YESAVAGE, J.A., TINKLENBERG, J.R., BERGER, P.A. and HOLLISTER, L.E. Vasodilators in senile dementia: a review of the literature. Arch. Gen. Psychiatry 1979: 36: 220-223.
5. BERDE, B. and STURMER, E. Introduction to the pharmacology of ergot alkaloids and related compounds as a basis for their therapeutic application. In *Ergot Alkaloids and Related Compounds*, B. Berde and H.O. Schild, Eds., Berlin, Springer-Verlag, 1978, 1-28.
6. CHOUINARD, G., ANNABLE, L., ROSS-CHOUINARD, A., OLIVIER, M. and FONTAINE, F. A double-blind placebo-controlled study of piracetam in elderly psychiatric patients. Psychopharm. Bull. 1981; 17: 129.
7. LEHMANN, H. Psychopharmacological approaches to the organic brain syndrome. Comprehens. Psychiatry 1983; 24: 412-430.
8. DAVIES, P. Neurotransmitter-related enzymes in senile dementia of the Alzheimer type. Brain Res. 1979; 171: 319-327.
9. COYLE, J.T., PRICE, D.L. and DE LONG, M.R. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 1983; 219: 1184-1190.
10. BRINKMAN, S.D., POMARA, N., GOODNICK, P.J., BARNETT, N. and DOMINO, E.F. A dose-ranging study of lecithin in the treatment of primary degenerative dementia (Alzheimer disease). J. Clin. Psychopharmacol. 1982; 2: 181-185.
11. DAVIS, K.L. and MOHS, R.C. Enhancement of memory processes in Alzheimer's disease with multiple-dose intravenous physostigmine. Amer. J. Psychiatry 1982; 139: 1421-1424.
12. DE WIED, D. Behavioral actions of neurohypophyseal peptides. Proc. Royal Soc. London (Biol.), 1980; 210: 183-195.
13. WHITE, L., CROVELLO, J.N., ROSENBERG, S.N. and NEIFITCH, J.A. Evaluation of isobaric oxygenation for the aged with cognitive impairment: Pilot study. J. Amer. Ger. Soc. 1975; 23: 80-85.

Treatment of Alzheimer's disease: new outlooks for the future

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Present therapeutic efforts in Alzheimer's Disease (AD) are based on either of two concepts: *first*, that one or more neuronal pharmacosystems are malfunctioning, whether they are intact or are partially depleted of neurons (1); *second*, that cerebral metabolism is diminished in a non-specific way(s). Drugs that enhance neurotransmitter function in remaining neural circuits have been tried in an effort to overcome the first hypothesized mechanism; metabolic enhancing agents, or "nootropic" drugs have been used to deal with the second (3).

Despite sporadic reports of barely detectable improvements with various drugs or drug combinations, therapeutic efforts have, in general, failed to produce improvement of clinical value. It is well to remember that, except for the extraordinary therapeutic success of dopaminergic agonists in Parkinsonism, no other degenerative neurologic disorder has responded to a similar strategy. We must, therefore, consider other therapeutic approaches that depend on different concepts of the etiology and pathogenesis of AD.

Our present knowledge of the cause of AD, and the mechanism by which its brain changes produce dementia is scant. The most likely possibilities are:

1) AD is a *degenerative disorder*, linked to aging, with *genetic loading*, influenced by *environmental factors* (2);
2) Ad causes both *losses* of neural elements, and *dysfunction* in remaining ones;
3) Ad affects neural elements both in a *diffuse* pattern, and more severely in *selectively vulnerable* systems.

Ideal therapeutic strategies would attack the underlying etiology of AD, preventing the pathogenetic process — be it biochemical or viral, toxic or genetic — from damaging the brain. Such approaches are wishful at best until we know more about the etiology of AD. *Secondary* strategies would attempt

to delay the onset, or slow the progress of the disease by eliminating environmental factors that *contribute* to its severity. At present, we have little idea of these contributing factors, although epidemiologic studies may provide some answers regarding the influence of diet, lifestyle, toxic exposures, etc.

Strategies currently approachable must attempt to *enhance* existing functions and *substitute* for lost capacities. These strategies attempt to use pharmacologic or other means to improve failing functions without removing the cause of disease. Although some pharmacotherapy tried to date falls into this category, much remains unexplored. For example, if dementia is due in part to interference with neuronal or synaptic plasticity, this process could be specifically facilitated. Our knowledge of plasticity has expanded considerably over the last 20 years, and it is now known that both ionic transport across membranes and protein synthesis are critical elements in synaptic plasticity. The functions, in turn, depend on calcium channel conductance, the presence of cAMP and protein kinase, and the integrity of molecular functions undelying protein synthesis (transcription, translation, etc.) (4). Attempts to improve synaptic plasticity must deal with these fundamental processes. Similarly, a decline in the ability of neurons to remodel their connections by nerve growth and sprouting may interfere with learning in AD, and may be susceptible to improvement by the use of nerve growth factors. Further, substitution of specific missing elements, selectively impaired by AD (such as the cholinergic neurons) may be attempted by brain transplantation techniques.

There are many opportunities to try strategies that can enhance existing brain function by favoring those neurobiologic processes that underlie memory and cognition. In the future, with a better understanding of the contributing factors and etiology of AD, we may devise more direct methods of treatment (5).

REFERENCES

1. DRACHMAN, D.A. and GLOSSER, G. (1981). In: "Strategies for the Development of an Effective Treatment for Senile Dementia", edited by T. Crook and S. Gershon, pp. 35-52, Mark Powley Associates, Inc., New Canaan.
2. DRACHMAN, D.A. (1983). In: "Aging of the Brain", edited by D. Samuel, S. Algeri, S. Gershon, D. Grimm and G. Toffano, pp. 19-32, Raven Press, New York.
3. FERRIS, S.A., REISBERG, B., CROOK, T. et al. (1982). In. "Alzheimer's Disease: A Report of Progress in Research", edited by S. Corkin, K. Davis, J. Growden, E. Usdin and R. Wurtman, pp. 475-482, Raven Press, New York.
4. KANDEL, E. (1978). A Cell-Biological Approach to Learning, Society for Neuroiscience, Bethesda.
5. LABBE, R., FIRL, A., MUFSAN, E. and STEIN, D.G. (1983). (Fetal Brain Transplants: Reduction of Cognitive Deficits in Rats with Frontal Cortex Lesions). Science, 221: 470-472.

Printed in Belgium

Normal Aging, Alzheimer's Disease and Senile Dementia

Aspects on Etiology, Pathogenesis, Diagnosis and Treatment

CHIEF EDITOR : C.G. GOTTFRIES

Editions de l'Université de Bruxelles

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Proceedings of two symposia
held at
The Collegium Internationale
Neuro-Psychopharmacologicum 14th Congress
June 22 and 23, 1984, Florence, Italy

I: Etiological and pathogenetic aspects
II: Diagnostic and treatment aspects

ÉDITIONS DE L'UNIVERSITÉ DE BRUXELLES

GROENINGHE PRINTING, 56 Buda, 8500 COURTRAI (Belgium)

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I.S.B.N. 2-8004-0873-1
D/1985/0171/21

Imprimé en Belgique

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Drugs of the Future 1999, 24(4): 417-424

CCC: 0377-8282/99

Review Article

Cholinergic therapies in Alzheimer's disease

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CONTENTS

Introduction

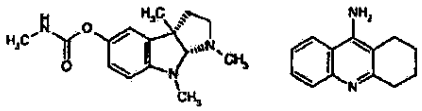
Alzheimer's disease (AD) is the most common cause of dementia in the elderly (1). The prevalence of AD at the age of 65 is approximately 10% and approaches 50% by the age of 85. The disease course is variable, but generally is characterized by a gradual and progressive decline in intellectual function and behavioral abnormalities in the absence of significant impairment of arousal. Despite the burgeoning information regarding the complex genetic and neuropathological basis of AD, its proximate cause remains unknown. Consequently, goals of disease prevention and neuroprotection remain elusive. In contrast, the rapidly increasing number of aged individuals in society ensures that the treatment goal of symptom amelioration will remain a crucial aspect of disease management. Here, we discuss some of the directions in drug development for AD based on cholinergic neurotransmission.

Over the past two decades, it has become well established that a disorder of cortical cholinergic innervation exists in AD (2-4). Several lines of evidence suggest that a cholinergic deficiency may contribute to cognitive and behavioral symptoms in AD. Low levels of markers of cholinergic function have been consistently described in cortical tissues in AD, including 30-90% reductions of choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of acetylcholine (ACh) (5-7). Acetylcholinesterase (AChE), the enzyme responsible for catabolism of ACh, and presynaptic cholinergic receptors are also deficient (7). Decreased levels of these cholinergic markers have been attributed to loss of neurons in the basal forebrain which provide diffuse cholinergic input to the entire cortical mantle, hippocampus and amygdala (8). Selective lesions of the cholinergic system in experimental animals, as well as naturally occurring lesions in humans, demonstrate a role for ACh in attention and memory. Anticholinergic drugs such as scopolamine, which block muscarinic receptors, also impair memory and result in confusional states in humans, which can be reversed by cholinomimetic agents such as physostigmine (9). Several studies have demonstrated correlation of dementia severity with the cholinergic deficiency and loss of synapses (10, 11). Finally, restoration of cholinergic function has been attempted in humans in recent years using AChE inhibitors as well as direct acting muscarinic agonists, with both approaches showing beneficial effects on cognition and, perhaps more surprisingly and dramatically, on behavior.

Augmentation of cholinergic neurotransmission might be accomplished in several different ways, including increased synthesis of ACh, decreased hydrolysis, increased release from the presynaptic terminal, *e.g.*, by inhibition of presynaptic cholinergic autoreceptors, and by direct stimulation of postsynaptic cholinergic receptors. Treatment with precursors of ACh such as choline and lecithin is ineffective (12, 13). The rate-limiting step in the synthesis of ACh is the high-affinity transport of choline across the neuronal membrane which shows saturation kinetics that may partially account for the minimal benefit seen with the precursors of ACh (14). In contrast, cholinergic drugs with other mechanisms of action are more promising and some have been shown to be effective. Some of the advances pertaining to the development of new cholinergic drugs, including those with varied mechanisms of action such as AChE inhibition, effect on presynaptic or postsynaptic receptors and release of ACh from the cholinergic terminal, are discussed below.

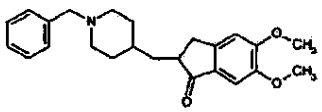
Acetylcholinesterase inhibitors

ACh released in the synaptic cleft is rapidly hydrolyzed by AChE. Blockade of hydrolysis results in increased levels of ACh and may partially correct the cholinergic deficiency seen in AD. AChE inhibitors (AChEIs) are broadly classified in three categories. These include: the amines such as physostigmine, donepezil and tacrine; the carbamates such as ENA-713; and the organophosphates such as metrifonate. The different AChEIs have unique mechanisms and durations of action.

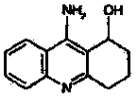


Physostigmine

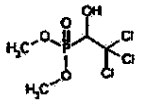
Tacrine



Donepezil



Velnacrine

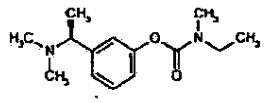


Metrifonate

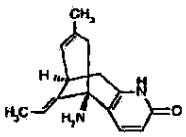
AChEIs have been extensively studied as treatment options for AD over the past two decades after the initial observations that physostigmine reverses the disruption of cognition produced by scopolamine in animals and humans. Several clinical studies of physostigmine have resulted in mild cognitive improvement but benefits have been limited by a narrow therapeutic window and gastrointestinal and orthostatic side effects (15, 16). Controlled release preparations of physostigmine offer a better pharmacokinetic profile and subtle but statistically significant benefits in a subset of patients. Tacrine treatment provided cognitive improvement in 5-40% of mild to moderate AD patients (17-19). Gastrointestinal side effects and hepatotoxicity were dose-related and frequently prevented dose escalation to 160 mg, the dosage for maximum proven efficacy on cognition (20). Tacrine also caused substantial improvements in multiple behavioral domains including anxiety, apathy, hallucinations, aberrant motor behavior and disinhibition (21). Behavioral improvement may underlie the observations that long-term treatment with tacrine may delay institutionalization (22). Donepezil, another amine AChEI, has a long half-life and appears to have moderate efficacy comparable to that produced by the maximum recommended dose of tacrine, although this AChEI does not produce hepatotoxicity and has fewer gastrointestinal side effects (23, 24).

At least 38 AChEIs are currently being studied worldwide in preclinical or clinical studies. Velnacrine, a major metabolite of tacrine, has been studied as an AChEI although this drug has significant hepatotoxicity (25-27). Metrifonate is in its last phase of development. It is a prodrug which is converted to its active metabolite dichlorvos, an irreversible AChEI (28). This drug has the advantage of slow onset of action and long-lasting inhibition of AChE, permitting once-daily administration (29). Rivastigmine (ENA-713) is a long-lasting AChEI which potentiates central cholinergic transmission at doses not associated with significant peripheral effects (30). Rivastigmine was first marketed in Switzerland and is available in more than 30 countries worldwide. It has been approved by the European Commission and is currently under review by the U.S. Food and Drug Administration. The drug is administered twice daily and is not hepatotoxic since it is decomposed by its action on the target enzyme, resulting in a phenolic derivative which is excreted via the kidneys after sulfate conjugation. The alkaloid huperzine A is a long duration AChEI which has been used in traditional medicine and may have less toxicity than physostigmine (31-33). Galanthamine is another natural alkaloid which is a long-acting, relatively selective AChEI with less butyrylcholinesterase (BChE) inhibitory activity (34, 35). This drug has the potential for significant gastrointestinal side effects, and its analogs are also being developed with more favorable effects. Phenserine is a novel AChEI related to physostigmine, but with a wide therapeutic window, long duration of action and low toxicity (36). A number of these AChEIs are expected to be approved for clinical use soon.

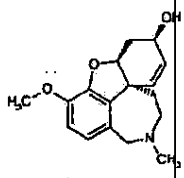
Important considerations in evaluating cholinomimetic treatment in general, and AChEIs in particular, include pharmacokinetic and pharmacodynamic properties of the AChEIs, as well as the biological heterogeneity of the patient population (37). For example, patients with diffuse Lewy body disease represent a subgroup of demented patients that respond well to AChEIs (38). In addition, AD patients who do not have apolipoprotein E4 show marked improvement in cognition when treated with tacrine (39). This improvement was found to be directly related to the relative preservation of ChAT and nicotinic receptor bind-



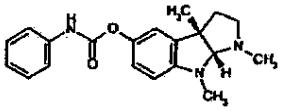
Rivastigmine



Huperzine A



Galanthamine



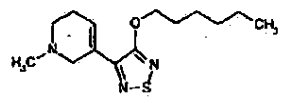
Phenserine

ing sites in the hippocampal formation and the temporal cortex. The most important factors in achieving a therapeutic response appear to be level of AChE inhibition, plasma drug concentration and optimal dosing (38). AChEIs are sometimes underdosed because of their peripheral cholinergic adverse effects and variable pharmacologic properties. An ideal AChEI is selective for brain cholinesterase(s), crosses the blood-brain barrier readily and has a prolonged duration of action. Cognitive responders are mostly individuals who have mild to moderate dementia. In contrast, patients with severe dementia may not have sufficient numbers of remaining cholinergic terminals necessary for ACh release and AChEI efficacy. Alternatively, postsynaptic effector systems may not be intact.

Some recent developments in the neurobiology of cholinesterases have implications for drug development. Two forms of ChEs have long been recognized in humans: AChE is the principal ChE responsible for the hydrolysis of ACh while the function of BChE is not well established (40, 41). In AD, AChE is decreased in several brain areas, but BChE increases in the cortex, plasma and cerebrospinal fluid. Both ChEs are present in senile plaques and neurofibrillary tangles, and may have a role in abnormal protein processing (42). Several molecular forms of both cholinesterases are now recognized, including globular and asymmetric types (14). The globular form G4 is the most widespread in the brain and is thought to mediate the degradation of ACh at cholinergic synapses (43). In AD, the G4 form has a possible presynaptic location and like other presynaptic cholinergic proteins is significantly reduced in AD. In contrast, the G1 form remains unchanged. Tacrine and physostigmine inhibit both G1 and G4 forms equally. However, rivastigmine is more potent in inhibiting the G1 form as compared to the G4 form and may offer additional benefits not seen with tacrine and physostigmine. Moreover, this drug is not only selective for brain, but is also more potent in inhibiting AChE in the cortex and hippocampus. Continuing advances in understanding molecular aspects of AChE and their role in AD will likely provide insights for design of new AChEIs.

Selective muscarinic agonists/antagonists

The central nervous system contains both nicotinic (nAChR) and muscarinic cholinergic receptors (mAChR) (44). The mAChR family has been emphasized in drug development for AD given its better established role in memory. The results of early clinical studies of nonselective first-generation muscarinic agonists, including arecoline, bethanecol, oxotremorine, pilocarpine and RS-86, were disappointing. These compounds possess low potency, significant peripheral parasympathetic side effects, short duration of action and poor oral bioavailability. Moreover, they show little or no specificity for different mAChR subtypes, several of which may have opposite actions on cholinergic function. Therefore, a clear understanding of the mAChR family of 5 receptors, M_1-M_5, is essential for more effective cholinergic therapies.

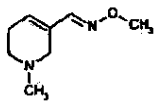


Xanomeline

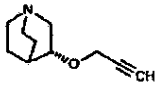
M_1 receptors are the major postsynaptic muscarinic receptors and have been viewed as a major target for cognition enhancing drugs (45). These receptors are most abundant in the hippocampus and neocortex, regions which are critical for memory and learning. There are generally low levels of this receptor subtype in peripheral tissues, which may lessen many of the typical side effects of AChEIs (e.g., gastrointestinal). Since the cortical M_1 receptors have a postsynaptic location, they may remain a potentially useful target even after degeneration of presynaptic terminals. However, a potential drawback is that there are questions about whether postreceptor signal transduction mechanisms are intact beyond these receptors (46, 47). Xanomeline is an M_1 agonist (48, 49) that was shown to produce moderate improvement in cognition in a recent double-blind, placebo-controlled study in AD (50, 51). Behavioral improvements were even more noteworthy. Psychosis, agitation, suspiciousness and vocal outbursts decreased significantly and in a dose-related manner. The drug was effective in preventing the emergence of these symptoms and in reducing those present before the start of therapy. Thus, M_1 agonists may acquire an important role in treating behavioral symptoms. This is a crucial aim for drug development in AD, since behavioral problems appear in more than 50% of patients, usually appearing late in the disease, and their refractory nature often leads to institutionalization (52-54).

There is also preclinical evidence that muscarinic stimulation with M_1 agonists may offer neuroprotection. For example, M_1 agonists influence the processing and secretion of amyloid precursor protein (APP) in a potentially less amyloidogenic manner (55, 56), and also decrease the phosphorylation state of tau which may retard formation of neurofibrillary tangles. Several other second-generation muscarinic agonists also appear promising and are in various stages of preclinical and clinical evaluation, including milameline, WAL-2014, AF-102B, YM-796 and PD-151832 (57).

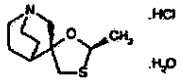
Some evidence suggests that M_2 receptors are presynaptically localized on cholinergic terminals. These M_2 "autoreceptors" function in a negative feedback loop, as synaptic ACh stimulates these receptors and inhibits further release of ACh. The therapeutic potential of drugs that inhibit M_2 autoreceptors is considerable for AD, since the effect would presumably lead to increased physiological release of ACh. Indeed, in preclinical studies, antagonists of M_2 receptors such as AF-DX-116 were shown to have beneficial effects on memory in animals (58).



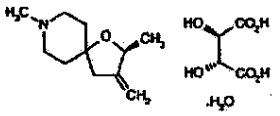
Milameline



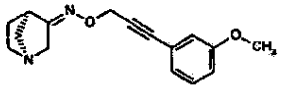
WAL-2014



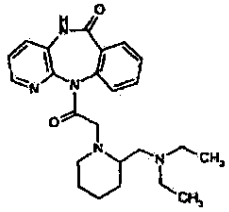
AF-102B



YM-796



PD-151832



AF-DX-116

However, the reduction of M_2 receptors in AD and the ongoing loss of presynaptic cholinergic terminals may limit the effectiveness of this approach. Moreover, M_2 receptors are also found pre- and postsynaptically on noncholinergic neurons. In addition, a general concern with M_2 selective drugs are the many possible side effects resulting from interactions with these receptors in peripheral tissues, *e.g.*, heart and gastrointestinal tract, where this receptor subtype is abundant.

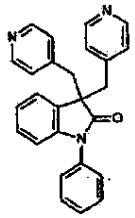
M_4 receptors and, to a lesser degree, M_3 receptors may remain relatively intact even in advanced AD (59). The potential therapeutic role of M_4 receptors is particularly intriguing as these receptors are increased in AD and appear to be localized presynaptically on excitation, associational and commissural projections in the hippocampus and, perhaps, other cortical regions. Drugs targeting these presynaptic sites might augment the corticocortical connections by increasing release of excitatory amino acid transmitters. In addition, the efficacy of xanomeline might relate to some of the recently discovered M_4 agonist properties of this compound (60). The prominence of M_4 receptor in basal ganglia also raises the possibility that M_4-selective drugs will be effective for subcortical dementias and movement disorders.

Acetylcholine releasers

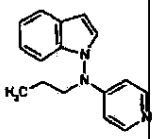
The development of drugs belonging to this class is still in its infancy. Linopirdine is an ACh releaser that has shown cognitive benefits in animals, but thus far not in humans. Although a randomized, controlled trial of linopirdine did not detect clinically relevant improvement after 6 months of treatment (61), the drug increased parietal blood flow in AD patients compared to controls (62). Like other drugs dependent on presynaptic mechanisms, ACh releasers will have potentially limited effects in the later stages of the disease as cholinergic terminals degenerate.

Novel combination therapy

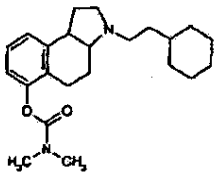
Deficiency of multiple neurotransmitters is known to occur in AD. In addition to the basal forebrain cholinergic nuclei, degeneration consistently affects cortical excitatory amino acid connections, certain peptidergic systems and frequently dopaminergic, serotonergic, histaminergic and noradrenergic projections to the cortex (63). Although degeneration of these systems may variably contribute to different symptoms (*e.g.*, psychosis, depression, sleep disruption), these multiple deficiencies may likely contribute to the cognitive impairment of AD. Hence, drugs with simultaneous cholinergic effects and other actions may have a synergistic role in AD treatment. Besipirdine is an analog of 4-aminopyridine which selectively blocks a potassium M-channel. In addition to being a weak cholinergic agonist, besipirdine has multiple other actions including neuronal presynaptic inhibition of norepinephrine, 5-HT and dopamine uptake (64). It is also an antagonist at the α_2 adrenoceptors. A recent treatment and withdrawal trial showed a trend of limited benefit (65). The higher potency of the drug for monoaminergic *versus* cholinergic receptors was thought to result in adverse



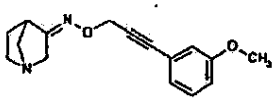
Linopirdine



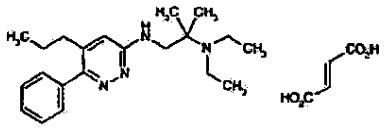
Besipirdine



Ro-46-5934



PD-142505



SR-46559

behavioral effects and possibly obscured any benefit expected using the global ratings. A different drug with lesser monoaminergic potency may result in more favorable effects.

The multiplicity of neurotransmitter interactions, including the presence of presynaptic mAChR on all terminals containing the other major neurotransmitters, raises the possibility that AChEIs may also exert their therapeutic effects via other mechanisms (66). Moreover, many AChEIs, including physostigmine, eptastigmine and donepezil, also raise the levels of dopamine and norepinephrine in the cortex. Combination therapy with AChEIs and a selective adrenergic α_2 antagonist such as idazoxan, which increases the level of norepinephrine, has been suggested as another model to replenish the multiple neurotransmitter deficiencies (67-69).

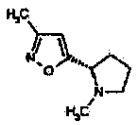
The combination of an M_1 agonist with an AChEI, both of which have shown clinical efficacy in AD, is a theoretical consideration which has not been studied in randomized clinical trials. While combination therapy has potential concerns with drug interactions and side effects, the possibility exists that differences in mechanisms of action will have complementary effects, *e.g.*, higher efficacy for improving cognition and behavioral disturbances. Likewise, the combination of a selective M_2 antagonist with an AChEI would theoretically enhance cholinergic function. Ro-46-5934, a novel agent with the combined action of AChE inhibition and M_2 antagonism, is in development. Muscarinic drugs with more agonist activity at M_1 receptors compared to M_2, such as PD-142505, and M_1 agonist but M_2 antagonist drugs, such as SR-46559, are other recent advances in experimental phase of development (57).

Nicotinic agonists

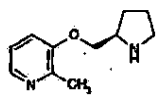
The nAChR comprise a family of ligand-gated ion channels (70). Each receptor consists of 5 subunits with significant genetic heterogeneity, resulting in potentially tremendous diversity of nAChR subtypes. The importance of heterogeneity of these receptors in the central and peripheral nervous systems becomes evident in the context of drug development to favorably stimulate cortical nAChR without producing unwanted effects in the peripheral nervous system. In the rat, blockade of nicotinic transmission with mecamylamine and blockade of muscarinic receptors with scopolamine results in far greater cognitive impairment than achieved with scopolamine alone (71). Moreover, many nicotinic receptor agonists have also been shown to increase levels of ACh, norepinephrine and dopamine. Stimulation of these receptors has also been shown to enhance memory, learning and attention in humans. Hence, one or more subtypes of nAChR might be good targets for new drugs as we acquire a better understanding of the neurobiology of these receptors.

Nicotinic receptors in the cortex and hippocampus decrease in number with aging but the reduction is far more prominent in dementing illnesses such as AD. A number of studies of AD have shown significant reduction in binding of nicotinic receptor sites in the hippocampus (72, 73). Initial work with stimulation of nAChR indicates that nicotine can improve some aspects of cognitive functions and, in particular, increase attention (74). Moreover, nicotinic receptor stimulation protects against β-amyloid toxicity in cultured rat neurons (75). Epidemiological studies of cigarette smoking have also shown a protective effect against AD (76, 77).

Possible side effects of nicotine include anxiety and depression, as well as cardiovascular, sleep and gastrointestinal problems. Ultimately, the positive and negative effects are likely to vary substantially depending on the receptor selectivity of each compound. Clinical trials will be necessary to clarify the therapeutic potential of nicotinic drugs. Several new nicotinic compounds are currently being evaluated. ABT-418 has been found to have cognition enhancing and anxiolytic effects when administered to AD patients (78). Its duration of action is short after a single fixed dose and the drug is being evaluated as a transdermal formulation to ensure optimal delivery. ABT-089 is another related compound that can be administered orally and is in initial phase of development (79,



ABT-418



ABT-089

80). Anabasine derivatives are selective nicotinic agonists undergoing preliminary evaluation, and they appear to have cytoprotective and cognition enhancing effects (81).

Conclusions

As our knowledge of the complex brain functions increases it appears that cholinergic drugs with nonselective mechanisms and with limited efficacy will be replaced or complemented by more selective drugs. Targeted drugs will likely enhance cholinergic transmission in selected tissues and more efficaciously. The interactions of multiple neurotransmitters and receptors will need to be considered for successful drug development. Judicious pharmacological manipulation of the muscarinic and nicotinic receptor subtypes and enhanced cholinomimetic effect has the potential of restoring or stabilizing a failing neurotransmission in AD, resulting in clinical improvement in cognition and behavior.

References

1. Evans, D.A., Funkenstein, H., Albert, M.S. et al. *Prevalence of Alzheimer's disease in a community population of older persons.* JAMA 1989, 262: 2551-6.

2. Cummings, J.L., Kaufer, D. *Neuropsychiatric aspects of Alzheimer's disease: The cholinergic hypothesis revisited.* Neurology 1996, 47: 876-83.

3. Bartus, R.T., Dean, R.L. III, Beer, B., Lippa, A.S. *The cholinergic hypothesis of geriatric memory dysfunction.* Science 1982, 217: 408-17.

4. Coyle, J.T., Price, D.L., DeLong, M.R. *Alzheimer's disease: A disorder of cortical cholinergic innervation.* Science 1983, 219: 1184-90.

5 Whitehouse, P.J., Price, D.L., Strubble, R.G., Clark, A.W., DeLong, M.R. *Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain.* Science 1982, 215: 1237-9.

6. Mash, D.C., Potter, L.T. *Autoradiographic localization of M_1 and M_2 muscarine receptors in the rat brain.* Neuroscience 1986, 19: 551-64.

7. Davies, P., Maloney, A.J.F. *Selective loss of central cholinergic neurons in Alzheimer's disease.* Lancet 1976, 2: 1403.

8. Whitehouse, P.J., Price, D.L., Clark, A.W., Coyle, J.T., DeLong, M.R. *Alzheimer disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis.* Ann Neurol 1981, 10: 122-6.

9. Drachman, D.A. *Memory and cognitive function in man: Does the cholinergic system have a specific role?* Neurology 1977, 27: 783-90.

10. Perry, E.K., Tomlinson, B.E., Blessed, G., Bergman, K., Gibson, P.H., Perry, R.H. *Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia.* Br Med J 1978, 2: 1457-9.

11. Terry, R.D., Masliah, E., Salmon, D.P. et al. *Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment.* Ann Neurol 1991, 30: 572-80.

12. Van Reekum, R., Black, S.E., Conn, D., Clarke, D. *Cognition-enhancing drugs in dementia: A guide to the near future.* Can J Psychiatry 1997, 42(Suppl. 1): S35-50.

13. Thal, L.J. *Cholinomimetic treatment of Alzheimer's disease.* Prog Brain Res 1996, 109: 299-309.

14. Cooper, J.R., Bloom, F.E., Roth, R.H. *Acetylcholine.* In: The Biochemical Basis of Neuropharmacology. Oxford University Press: New York 1996, 194-225.

15. Asthana, S., Raffaele, K.C., Berardi, A. et al. *Treatment of Alzheimer disease by continuous intravenous infusion of physostigmine.* Alzheimer Dis Assoc Disord 1995, 9: 223-32.

16. Thal, L.J., Schwartz, G., Sano, M. et al. *A multicenter double-blind study of controlled-release physostigmine for the treatment of symptoms secondary to Alzheimer's disease.* Neurology 1996, 47: 1389-95.

17. Eagger, S.A., Levy, R., Sahakian, B.J. *Tacrine in Alzheimer's Disease.* Lancet 1991, 337: 990-2.

18. Farlow, M., Gracon, S.I., Hershey, L.A. et al. *A controlled trial of tacrine in Alzheimer's disease.* JAMA 1992, 268: 2523-9.

19. Schneider, L.S. *Clinical pharmacology of aminoacridines in Alzheimer's disease.* Neurology 1993, 43(Suppl. 4): S64-79.

20. Davis, K.L., Powchik, P. *Tacrine* Lancet 1995, 345: 625-30.

21. Kaufer, D.I., Cummings, J.L., Christine, D. *Effect of tacrine on behavioral symptoms in Alzheimer's disease: An open-label study.* J Geriatr Psychiatry Neurol 1996, 9: 1-6.

22. Knopman, D., Schneider, L., Davis, K. et al. *Long-term tacrine (Cognex) treatment: Effects on nursing home placement and mortality.* Neurology 1996, 47: 166-77.

23. Goldmacher, D.S. *Donepezil (Aricept) therapy for Alzheimer's disease.* Compr Ther 1997, 23: 492-3.

24. Rogers, S.L., Doody, R., Mohs, R., Friedhoff, L.T. *E2020 produces both clinical global and cognitive test improvement in patients with mild to moderately severe Alzheimer's disease: Results of a 30-week phase III trial.* Neurology 1996, 46(Suppl.): A217.

25. Zemlan, F.P., Keys, M., Richter, R.W., Strub, R.L. *Double-blind placebo-controlled study of velnacrine in Alzheimer's disease.* Life Sci 1996, 58: 1823-32.

26. Zemlan, F.P. et al. *Velnacrine for the treatment of Alzheimer's disease: A double-blind, placebo-controlled trial.* J Neural Transm 1996, 103: 1105-16.

27. Antuono, P.G. et al. *Effectiveness and safety of velnacrine for the treatment of Alzheimer's disease.* Arch Intern Med 1995, 155: 1766-72.

28. Hinz, V.C., Grewig, S., Schmidt, B.H. *Metrilonate induces cholinesterase inhibition exclusively via slow release of dichlorvos.* Neurochem Res 1996, 21: 331-7.

29. Unni, L.K., Womack, C., Hannant, M.E., Becker, R.E. *Pharmacokinetics and pharmacodynamics of metrilonate in humans.* Meth Find Exp Clin Pharmacol 1994, 16: 285-9.

30. Sramek, J.J., Anand, R., Wardle, T.S., Irwin, P., Hartman, R.D., Cutler, N.R. *Safety/tolerability trial of SDZ ENA 713 in patients with probable Alzheimer's disease.* Life Sci 1995, 58: 1201-7.

31. Zhu, X.D., Giacobini, E. *Second generation cholinesterase inhibitor: Effect of (-)-huperzine A on cortical biogenic amines.* J Neurosci Res 1995, 41: 828-35.

32. Ved, H.S., Koenig, M.L., Dave, J.R., Doctor, B.P. *Huperzine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate.* NeuroReport 1997, 8: 963-8.

33. Cheng, D.H., Ren, H., Tang, X.C. *Huperzine A, a novel promising acetylcholinesterase inhibitor.* NeuroReport 1996, 8: 97-101.

34. Bores, G.M., Huger, F.P., Petko, W. et al. *Pharmacological evaluation of novel Alzheimer's disease therapeutics: Acetylcholinesterase inhibitors related to galanthamine.* J Pharmacol Exp Ther 1996, 277: 728-38.

35. Harvey, A.L. *The pharmacology of galanthamine and its analogues.* Pharmacol Ther 1995, 68: 113-28.

36. Iijima, S., Grieg, N.H., Garofalo, P. et al. *Phenserine: A physostigmine derivative that is a long acting inhibitor of cholinesterase and demonstrates a wide dose range for attenuating a scopolamine-induced learning impairment of rats in a 14-unit T-maze.* Psychopharmacology 1993, 112: 415-20.

37. Eagger, S.A., Harvey, R.J. *Clinical heterogeneity: Responders to cholinergic therapy.* Alzheimer Dis Assoc Disord 1995, 9(Suppl. 2): 37-42.

38. Schneider, L.S., Farlow, M.R. *Predicting response to cholinesterase inhibitors in Alzheimer's disease.* CNS Drugs 1995, 42: 114-24.

39. Poirier, J., Delisle, M-C., Quirion, R. et al. *Apolipoprotein epsilon4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer's disease.* Proc Natl Acad Sci USA 1995, 92: 12260-4.

40. Geula, C., Mesulam, M. *Special properties of cholinesterases in the cerebral cortex of Alzheimer's disease.* Brain Res 1989, 498: 185-9.

41. Geula, C., Mesulam, M.M. *Cholinesterases and the pathology of Alzheimer disease.* Alzheimer Dis Assoc Disord 1995, 9(Suppl. 2): 23-8.

42. Mesulam, M.M., Geula, C., Moran, A. *Anatomy of cholinesterase inhibition in Alzheimer's disease: Effect of physostigmine and tetrahydroaminoacridine on plaques and tangles.* Ann Neurol 1987, 22: 683-91.

43. Enz, A., Amstutz, R., Boddeke, H., Gmelin, G., Malanowski, J. *Brain selective inhibition of acetylcholinesterase: A novel approach to therapy for Alzheimer's disease.* Prog Brain Res 1993, 98: 431-8.

44. Goyal, R.K. *Muscarinic receptor subtypes: Physiology and clinical implications.* New Eng J Med 1989, 321: 1022-9.

45. Levey, A.I., Kitt, C.A., Simonds, W.F., Price, D.L., Brann, M.R. *Identification and localization of muscarinic acetylcholine receptor proteins in brain with subtype-specific antibodies.* J Neurosci 1991, 11: 3218-26.

46. Jope, R.S., Song, L., Powers, R.E. *Cholinergic activation of phosphoinositide signaling is impaired in Alzheimer's disease brain.* Neurobiol Aging 1997, 18: 111-20.

47. Winblad, B., Messamore, E., O'Neill, C., Cowburn, R. *Biochemical pathology and treatment strategies in Alzheimer's disease: Emphasis on the cholinergic system.* Acta Neurol Scand 1993, (Suppl. 149): 4-6.

48. Bymaster, F.P., Wong, D.T., Milch, C.H. et al. *Neurochemical effects of the M_1 muscarinic agonist xanomeline (LY246708/NNC11-0232).* J Pharmacol Exp Ther 1994, 269: 282-9.

49. Shannon, H.E., Bymaster, F.P., Calligaro, D.O. et al. *Xanomeline: A novel muscarinic receptor agonist with functional selectivity for M_1 receptors.* J Pharmacol Exp Ther 1994, 269: 271-81.

50. Bodick, N.C., Offen, W.W., Levey, A.I. et al. *Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease.* Arch Neurol 1997, 54: 465-73.

51. Bodick, N.C., Offen, W.W., Shannon, H.E. et al. *The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease.* Alzheimer Dis Assoc Disord 1997, 11(Suppl. 4): S16-22.

52. Reisberg, B., Borenstein, J., Salob, S.P., Ferris, S.H., Franssen, E., Georgotas, A. *Behavioral symptoms in Alzheimer's disease: Phenomenology and treatment.* J Clin Psychiatry 1987, 48 (Suppl. 5): 9-15.

53. Cummings, J.L. *The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients.* Neurology 1997, 48(Suppl. 6): S10-6.

54. O'Donnell, B.F., Drachman, D.A., Barnes, H.J., Peterson, K.E., Swearer, J.M., Lew, R.A. *Incontinence and troublesome behaviors predict institutionalization in dementia.* J Geriatr Psychiatry Neurol 1992, 5: 45-52.

55. DeLapp, N.W., Eckols, K., Bymaster, F.P., Milch, C.H., Shannon, H.E., Ward, J.S. *The m_1 agonist xanomeline potently stimulates APPs release from CHO-m_1 cells.* Life Sci 1995, 56: 1024.

56. Nitsch, R.M., Slack, B.E., Wurtman, R.J., Growden, J.H. *Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors.* Science 1992, 258: 304-7.

57. Giacobini, E. *Cholinesterase inhibitors do more than inhibit cholinesterase.* In: Alzheimer Disease: From Molecular Biology to Therapy. Becker, R., Giacobini, E. (Eds.). Birkhauser: Boston 1997, 187-204.

58. Packard, M.G., Regenold, W., Quirion, R., White, N.M. *Post-training injection of the acetylcholine M_2 receptor antagonist AF-DX 116 improves memory.* Brain Res 1990, 524: 72-6.

59. Rodriguez-Puertas, R., Pascual, J., Vilaro, T., Pazos, A. *Autoradiographic distribution of M_1, M_2, M_3, and M_4 muscarinic receptor subtypes in Alzheimer's disease.* Synapse 1997, 26: 341-50.

60. DeLapp, N., Butler, T., Thomsen, C. et al. *Comparison of functional muscarinic m_2 and m_4 activity for the m_1-agonist xanomeline and four other clinical candidates for Alzheimer's disease.* Soc Neurosci 1997, 23: 1751.

61. Rockwood, K., Beattie, L., Eastwood, M.R. et al. *A randomized, controlled trial of linopirdine in the treatment of Alzheimer's disease.* Can J Neurol Sci 1997, 24: 140-5.

62. Van Dyck, C.H., Lin, C.H., Robinson, R. et al. *The acetylcholine releaser linopirdine increases parietal regional cerebral blood flow in Alzheimer's disease.* Psychopharmacology 1997, 132: 217-26.

63. Mesulam, M.M. *The systems-level organization of cholinergic innervation in the cerebral cortex and its alterations in Alzheimer's disease.* Prog Brain Res 1996, 109: 285-97.

64. Hubbard, J.W., Nordstrom, S.T., Smith, C.P. et al. *α-Adrenergic activity and cardiovascular effects of besipirdine HCl (HP 749) and metabolite P 7480 in vitro and in the conscious rat and dog.* J Pharmacol Exp Ther 1997, 281: 337-46.

65. Huff, F.J., Antuono, P.G., Delagandara, J.E. et al. *A treatment and withdrawal trial of besipirdine in Alzheimer disease.* Alzheimer Dis Assoc Disord 1996, 10. 93-102.

66. Hakansson, L. *Mechanism of action of cholinesterase inhibitors in Alzheimer's disease.* Acta Neurol Scand 1993, (Suppl. 149): 7-9.

67. Camacho, F., Smith, C.P., Vargas, H.M., Winslow, J.T. *α_2-Adrenoceptor antagonists potentiate acetylcholinesterase inhibitor effects on passive avoidance learning in the rat.* Psychopharmacology 1996, 124: 347-54.

68. Goodwin, G.M., Conway, S.C., Peyro-Saint-Paul, H., Glabus, M.F., O'Carroll, R.E., Ebmeier, K.P. *Executive function and uptake of ^{99m}Tc-exametazime shown by single photon emission tomography after oral idazoxan in probable Alzheimer-type dementia.* Psychopharmacology 1997, 131: 371-8.

69. Giacobini, E. *New trends in cholinergic therapy for Alzheimer disease: Nicotinic agonists or cholinesterase inhibitors?* Prog Brain Res 1996, 109: 311-23.

70. Court, J., Clementi, F. *Distribution of nicotinic subtypes in human brain.* Alzheimer Dis Assoc Disord 1995, 9(Suppl. 2): 6-14.

71. Sunderland, T., Molchan, S.E., Little, J.T., Bahro, M., Putnam, K.T., Weingartner, H. *Pharmacologic challenges in Alzheimer's disease and normal controls: Cognitive modeling in humans.* Alzheimer Dis Assoc Disord 1997, 11(Suppl. 4): S23-6.

72. Perry, E.K., Perry, R.H., Smith, C.J. et al. *Nicotinic receptor abnormalities in Alzheimer's disease and Parkinson's disease.* J Neurol Neurosurg Psychiatry 1987, 50: 806-9.

73. Whitehouse, P.J. *Cholinergic therapy in dementia.* Acta Neurol Scand 1993, (Suppl. 149): 42-5.

74. Lawrence, A.D., Sahakian, B.J. *Alzheimer disease, attention, and the cholinergic system.* Alzheimer Dis Assoc Disord 1995, 9(Suppl. 2): 43-9.

75. Kihara, T., Shimohama, S., Sawada, H. et al. *Nicotinic receptor stimulation protects neurons against beta-amyloid toxicity.* Ann Neurol 1997, 42 159-63.

76. Van Duijn, C.M., Hofman, A. *Relation between nicotine intake and Alzheimer's disease.* Br Med J 1991, 302: 1491-4.

77. Graves, A.B., Van Duijn, C.M., Chandra, V. et al. *Alcohol and tobacco consumption as risk factors for Alzheimer's disease: A collaborative re-analysis of case-control studies.* Int J Epidemiol 1991, 20(Suppl. 2): S48-57.

78. Americ, S.P., Sullivan, J.P., Decker, M.W. et al. *Potential treatment of Alzheimer disease using cholinergic channel activators (ChCAs) with cognitive enhancement, anxiolytic-like, and cytoprotective properties.* Alzheimer Dis Assoc Disord 1995, 9(Suppl. 2): 50-61.

79. Sullivan, J.P., Donnelly-Roberts, D., Briggs, C.A. et al. *ABT-089 [2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine]: I. A potent and selective cholinergic channel modulator with neuroprotective properties.* J Pharmacol Exp Ther 1997, 283: 235-46.

80. Decker, M.W., Bannon, A.W., Curson, P. et al. *ABT-089 [2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride]: II. A novel cholinergic channel modulator with effects on cognitive performance in rats and monkeys.* J Pharmacol Exp Ther 1997, 283: 247-58.

81. Decker, M.W., Brioni, J.D. *Neuronal nicotinic receptors: Potential treatment of Alzheimer's disease with novel cholinergic channel activators.* In: Pharmacological Treatment of Alzheimer's Disease. Brioni, J.D., Decker, M.W. (Eds.). Wiley-Liss, Inc.: New York 1997, 433-59.

EXHIBIT 12

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European Resident Partner

November 8, 1990

Dr. Bonnie Davis
17 Seacrest Drive
Huntington, New York 11743

Dear Dr. Davis:

RE: AGREEMENT WITH CIBA-GEIGY

We enclose herewith a copy of the final version of the above. As agreed, we are retaining the original for safe keeping.

Very truly yours,

John Richards

JR:ct
Enc.

Plaintiff's Exhibit
PX - 305

LICENSE AGREEMENT

LICENSE AGREEMENT made this 28th day of September 1990, by and between CIBA-GEIGY Corporation, a New York corporation, having offices located at 556 Morris Avenue, Summit, New Jersey 07901 (hereinafter "CIBA-GEIGY"), and Intelligen Corporation, a New York corporation, having an address of P.O. Box 157, Cold Spring Harbor, New York 11724 (hereinafter "Intelligen").

WITNESSETH:

WHEREAS, Intelligen is the owner, by way of assignment from Dr. Bonnie Davis ("Davis"), of United States Patent 4,663,318, issued on May 5, 1987, claiming the use of galanthamine and its pharmaceutically acceptable acid addition salts in the treatment of Alzheimer's Disease and related dementias;

WHEREAS, Intelligen is desirous of granting an exclusive license in the Territory under the aforesaid patent and the Know-How relating to it;

WHEREAS, CIBA-GEIGY wishes to obtain an exclusive license in the Territory, with the right to grant sublicenses, under said patent and the Know-How relating to it;

NOW, THEREFORE, in consideration of the premises and of the mutual covenants and obligations herein contained, the parties hereto agree as follows:

ARTICLE 1 - Definitions:

1.1 "Agreement Period" shall mean the period of time commencing upon the execution of this Agreement and ending (unless sooner terminated pursuant to this Agreement) on the date of expiration of the Patent Rights, as extended, or ten (10) years after first commercial marketing of Product in the Territory, whichever is greater.

1.2 "Know-How" shall mean all technology, formulae, trade secrets, technical, toxicological, pharmacological, scientific and/or medical data and any other information or experience (including, but not limited to, preclinical or clinical data), owned, controlled, possessed or received (from anyone except CIBA-GEIGY) by Intelligen or Davis that has been imparted to CIBA-GEIGY by Intelligen or Davis as of the date of execution of this Agreement specifically relating to the Product and which it or she is at liberty to disclose, as well as any improvements or modifications to the Know-How owned, controlled, possessed or received by Intelligen or Davis as of the date of execution of this Agreement and which it or she is at liberty to disclose, including, but not limited to, such data or information which will allow CIBA-GEIGY or its sublicensees to efficiently manufacture, use or sell Product. For the avoidance of doubt, it is

expressly agreed that data relating solely to analogues of galanthamine do not fall within the definition of Know-How.

1.3 "Product" shall mean the compound 4a, 5, 9, 10, 11, 12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro [3a, 3, 2-ef] [2] benzazepin-6-ol, also known as galanthamine, its pharmaceutically acceptable acid addition salts and any finished dosage form thereof.

1.4 "Net Sales" shall mean the amount billed by CIBA-GEIGY or its sublicensees to third parties for the sale of Product, less cash discounts and/or quantity discounts allowed; credits for customers; returns and allowances; charges for freight handling and transportation separately billed; and sales, use, inventory and storage taxes incurred.

1.5 "Patent Rights" shall mean all of Intelligen's right, title and interest in and to United States Patent 4,663,318, issued on May 5, 1987, and any continuation, continuation-in-part, division, substitution, reissue or reexamination thereof, under which a reasonable claim of infringement could be asserted by Intelligen against the use or sale of the Product by an unlicensed party. For the avoidance of doubt, it is agreed that Patent Rights do not extend to any continuation-in-part that makes no claim: (a) to galanthamine or a salt thereof or (b) to any use of galanthamine or a salt thereof.

1.6 "Territory" shall mean the United States of America and its territories and possessions.

1.7 "NDA" shall mean a New Drug Application, as defined in the Federal Food, Drug and Cosmetic Act, and applicable Regulations promulgated thereunder.

1.8. "CPI" shall mean the Consumer Price Index for All Urban Consumers using the figure for "all items" (1982-84 = 100), issued by the United States Bureau of Labor Statistics.

1.9. "Affiliates" shall mean all corporations, partnerships, joint ventures or other business entities which, directly or indirectly, are controlled by, control or are under common control with, CIBA-GEIGY. For this purpose, the meaning of the word "control" shall include, but not be limited to, ownership of fifty percent (50%) or more of the voting shares or interest in such corporation, partnership, joint venture or other business entity.

1.10 "Marketing Exclusivity" shall mean a period of non-patent marketing exclusivity granted pursuant to the terms of the Drug Price Competition and Patent Term Restoration Act of 1984, and any applicable Regulations promulgated thereunder.

1.11 "Dollar" means constant 1990 dollars. Wherever a payment due according to this Agreement is expressed in dollars, said payment shall be adjusted to take account of the change in value of the dollar according to the following formula:

sum payable = $\frac{\text{sum expressed in Agreement x CPI at time when due}}{\text{CPI for 1990}}$

1.12 "New Know-How" shall mean any and all new, further or unique technology, formulae, trade secrets, technical, toxicological, pharmacological, scientific and/or medical data, or any other tangible information or experience (including, by way of example, preclinical or clinical data) specifically relating to the manufacture, use or sale of the Product, owned, controlled, possessed or received by Intelligen or Davis after the date of execution of this Agreement and which it or she is at liberty to disclose. Such "New Know-How" shall include, but not be limited to, method(s) of extraction or synthesis specific to galanthamine, patent(s) or other tangible development(s). "New Know-How" shall further include developments for more general application useful in the development of the Product, including any new patient clinical rating scales development by Davis for assessing Alzheimer's Disease.

ARTICLE 2 - Grant:

2.1 Intelligen hereby grants to CIBA-GEIGY under the Patent Rights and the Know-How an exclusive license in the Territory, with the right to grant sublicenses, to make, have made, use and sell Product during the Agreement Period. Neither CIBA-GEIGY nor its Affiliates shall have any right to use the licensed Know-How, or any information supplied by Intelligen or Davis to CIBA-GEIGY pursuant to Article 3.3 or any New Know-How licensed to CIBA-GEIGY pursuant to

Article 2.5 of this Agreement after the date of execution of this Agreement, to facilitate sales of Product outside the Territory.

2.2 Intelligen represents and warrants that it is the owner of the Patent Rights and the Know-How, and has the right to grant the license referred to in Article 2.1 of this Agreement. Without limitation of the foregoing, Intelligen and Davis further represent and warrant that, to the best of their knowledge, neither the practice of the Patent Rights and the Know-How, nor the exercise of the rights granted in Articles 2.1 or 2.3 of this Agreement to CIBA-GEIGY or its sublicensees, infringe any patent or other rights of any third party.

2.3 In the event that Intelligen or Davis shall obtain a patent on the Know-How in the Territory, Intelligen and/or Davis grant to CIBA-GEIGY an exclusive license in the Territory, with the right to grant sublicenses, consistent with the terms of this Agreement and without additional royalty payments other than as set forth in this Agreement, to make, have made, use and sell Product under such patent. Intelligen and/or Davis further grant to CIBA-GEIGY a non-exclusive, royalty-free license under any other licensable patent rights it or she owns, controls, has the right to own, or the right to control, but only to the extent necessary for CIBA-GEIGY to make, have made, use or sell Product in the Territory.

2.4 Except as set forth in Article 7.2 of this Agreement, at the end of the Agreement Period, CIBA-GEIGY shall continue to have, in the

Territory, a perpetual, royalty-free, non-exclusive license to make, have made, use and sell Product and to practice the Know-How.

2.5 In the event that Intelligen or Davis make, receive, own, control or obtain any New Know-How, Intelligen and/or Davis agree to disclose said New Know-How to CIBA-GEIGY in writing, and provide CIBA-GEIGY with the first right of refusal to negotiate a license relating to said New Know-How. CIBA-GEIGY shall, within ninety (90) days of the receipt of such disclosure of said New Know-How from Intelligen or Davis, advise Intelligen or Davis as to whether or not it elects to enter into negotiations for such a license. In the event that CIBA-GEIGY so elects, the parties hereto shall negotiate such a license, in good faith, on mutually agreeable terms and conditions.

ARTICLE 3 - Payments and Development Plan:

3.1 In consideration of the rights granted in Article 2 of this Agreement, CIBA-GEIGY shall pay to Intelligen:

(a) Two hundred and fifty thousand dollars ($250,000.00) within thirty (30) days of the date of execution of this Agreement;

(b) One Hundred Thousand Dollars ($100,000.00) per year, payable in installments of twenty-five thousand dollars ($25,000.00) three (3) months from the date of execution of this Agreement, and twenty-five thousand dollars ($25,000.00) every three (3) months thereafter, provided each succeeding

three (3) month period occurs prior to the filing of an NDA by CIBA-GEIGY for the Product. The sum payable is calculated according to the following formula, which increases the yearly total payment by five percent (5%), adjusted to 1990 constant dollars by reference to the CPI:

Payment for each
quarter in year = $25,000.00 x $(1.05)^{n}$
"n"

where "n" is the number of whole years that have elapsed since execution of this Agreement.

Said payments shall cease upon the filing of an NDA by CIBA-GEIGY and during the time while such NDA is pending.

3.2 Three (3) distinct Development Plans for the Product are attached hereto as Exhibit A and incorporated herein by reference. Said Development Plans set forth the milestones reasonably to be achieved by CIBA-GEIGY during the Agreement Period and include, among other things, a planned NDA submission date (hereinafter "Filing Date"). It is expressly agreed by the parties that it is impossible to determine, at the time of execution of this Agreement, which of the attached Development Plans will become the final Development Plan for the Product due to the uncertainty, among other things, of the clinical studies necessary for the submission of an NDA, and other factors outside of the control of the parties hereto such as the

response of the United States Food and Drug Administration to any proposed clinical development plan for the Product. In light of said uncertainty, the parties agree that the determination of the final Development Plan shall be held in abeyance with the explicit understanding that CIBA-GEIGY will utilize that Development Plan which will allow the earliest submission of an approvable NDA under all of the circumstances and that CIBA-GEIGY shall notify Intelligen of its determination as soon as reasonably possible. In the event that CIBA-GEIGY has not filed an NDA on or before the Filing Date included in the Development Plan ultimately adopted hereunder, CIBA-GEIGY shall pay to Intelligen the sum of four hundred thousand dollars ($400,000.00) unless CIBA-GEIGY has not filed the NDA on or before said Filing Date because of reasons outside of the control of CIBA-GEIGY (including, but not limited to, new or changed regulatory requirements of the United States Food and Drug Administration not required as of the date of execution of this Agreement; unexpected adverse drug reactions to Product; unexpected toxicological results; safety or efficacy problems arising out of clinical trials different than expected) or force majeure as defined in Article 12 of this Agreement. The Development Plans attached hereto are explicitly premised on the assumption that a supply of Product is immediately available, and the Development Plans will be adjusted accordingly based upon the availability of Product. In no event, however, shall the commencement of the Development Plan be delayed by more than six (6) months from the date of execution of this Agreement. In the event that the parties do not agree upon what constitutes "reasons outside of the control of CIBA-GEIGY", as set forth above, the parties hereto

agree to take such issue (but only such issue) to arbitration by a single arbitrator chosen by the agreement of the parties, whose decision shall be final and binding. In the event that the parties cannot agree on an arbitrator, they will jointly request the American Arbitration Association to appoint an arbitrator. The fees payable to such arbitrator shall be shared equally by the parties.

3.3 During the period of time covered by the Development Plan, CIBA-GEIGY shall provide Intelligen with written reports of the progress and results of the development of the Product on a semi-annual basis. Additionally, semi-annual meetings shall be held between representatives of CIBA-GEIGY and Intelligen to discuss such progress and results of the development of the Product. CIBA-GEIGY acknowledges the expertise of Davis regarding galanthamine in the treatment of Alzheimer's Disease and related dementias, and shall reasonably consider suggestions made by her regarding the development of the Product. Any such suggestion or idea provided by Davis during such meetings shall not be deemed New Know-How for the purposes of Article 2.5 of this Agreement. Notwithstanding the foregoing, any and all decisions regarding the development of the Product, including the determination of which Development Plan shall be utilized, shall be at the sole direction and control of CIBA-GEIGY. Davis shall not be deemed an employee of, or independent contractor consultant to, CIBA-GEIGY by virtue of the foregoing.

3.4 All payments made by CIBA-GEIGY to Intelligen pursuant to Articles 3.1(b) and 3.2 of this Agreement shall be credited against

any and all royalty obligations owed by CIBA-GEIGY to Intelligen pursuant to Article 4 of this Agreement. Notwithstanding the foregoing, no such credit shall exceed the sum of twenty percent (20%) of any royalty due to Intelligen from CIBA-GEIGY pursuant to Article 4 of this Agreement during any particular year of the Agreement Period during which royalties are to be paid.

ARTICLE 4 - Royalties:

4.1 CIBA-GEIGY recognizes (in addition to the value of the Know-How rights) the respective values of the Patent Rights and Marketing Exclusivity rights being obtained hereunder and, further, recognizes that the possibility exists that the life of the Patent Rights may expire prior to the expiration of a period of Marketing Exclusivity obtained for the product. Therefore, in consideration of the rights granted in Article 2 of this Agreement, and in addition to the payments described in Article 3 of this Agreement, CIBA-GEIGY shall pay to Intelligen, during the Agreement Period, a royalty calculated as follows:

(a) The sum of seven percent (7%) of Net Sales of Product during the life of the Patent Rights, or any extension thereof, or period of Marketing Exclusivity, whichever period is longer, obtained by CIBA-GEIGY pursuant to this Agreement; or,

(b) The sum of five percent (5%) of Net Sales of Product as a Know-How royalty during the period, if any, between the

expiration of the Patent Rights, as extended, or Marketing Exclusivity, whichever period is longer, and the expiration of the Agreement Period, during which CIBA-GEIGY retains a market share of greater than ninety percent (90%) of sales of the Product in the Territory as determined by the records maintained by CIBA-GEIGY; or,

(c) The sum of three percent (3%) of Net Sales of Product as a Know-How royalty during the period, if any, between the expiration of the Patent Rights, as extended, or Marketing Exclusivity, whichever period is longer, and the expiration of the Agreement Period, during which CIBA-GEIGY retains a market share of less than or equal to ninety percent (90%) of sales of the Product in the Territory as determined by the records maintained by CIBA-GEIGY.

4.2 Commencing in the first full calendar year after the first commercial sale of Product by CIBA-GEIGY in the Territory, CIBA-GEIGY shall pay Intelligen a minimum annual royalty pursuant to Article 4.1 of this Agreement of two hundred fifty thousand dollars ($250,000.00). Said minimum annual royalty shall increase by the sum of fifty thousand dollars ($50,000.00) per year during the second, third and fourth full calendar years thereafter and shall increase by the sum of one hundred thousand dollars ($100,000.00) in the fifth full calendar year thereafter to a minimum annual royalty of five hundred thousand dollars ($500,000.00) during that fifth and subsequent full calendar years thereafter in which CIBA-GEIGY shall be obligated to pay

royalties at the rate of seven percent (7%) of Net Sales of Product pursuant to Article 4.1(a) of this Agreement. No minimum annual royalty shall be payable by CIBA-GEIGY to Intelligen during any full calendar year of the Agreement Period in which CIBA-GEIGY shall be obligated to pay royalties at the rate of five percent (5%) or three percent (3%) of Net Sales of Product pursuant to Articles 4.1(b) or 4.1(c) of this Agreement.

4.3 A Product shall be deemed to have been sold when shipped and billed in a bona-fide, arm's length transaction between unrelated parties. Sales between or among CIBA-GEIGY and its sublicensees shall not be subject to royalty hereunder, but in such cases shall be calculated upon CIBA-GEIGY's or its sublicensees' Net Sales of Product to an independent third party. Royalties shall accrue hereunder only once in respect of the same unit of Product. CIBA-GEIGY shall be responsible to Intelligen for payments due to Intelligen for sales by any sublicensee and shall make such payments when they become due regardless of whether CIBA-GEIGY has itself received payment from a sublicensee for the period in question.

ARTICLE 5 - Payments and Records:

5.1 Within sixty (60) days after the end of each calendar quarter during the Agreement Period, CIBA-GEIGY shall pay to Intelligen the royalty payment due under this Agreement for said calendar quarter. The sum of such payments during each calendar year in which Intelligen is entitled to a minimum annual royalty pursuant

to Article 4.2 of this Agreement shall be no less than the minimum annual royalty for that calendar year, less any credit due CIBA-GEIGY pursuant to Article 3.4 of this Agreement.

5.2 CIBA-GEIGY shall accompany said payment with a written accounting setting forth the basis for, and its computation of, royalties under this Agreement for said calendar quarter.

5.3 CIBA-GEIGY shall keep full, true and accurate books of account and other records containing all particulars which may be necessary to ascertain properly and verify the reports made and the royalties payable by it hereunder. During the Agreement Period, and within one (1) year thereafter, Intelligen shall have the right, to be exercised no more than one (1) time per calendar year, to have, at its own expense, an independent certified public accountant to which CIBA-GEIGY has no reasonable objection inspect, during regular business hours, said books, records, and all supporting data for not more than two (2) preceding years; provided, however, that such accountant shall keep confidential any information obtained during such inspection and shall report to Intelligen only on the accuracy of the reports made and the amounts of royalties due and payable hereunder. In the event that any such inspection or audit reveals an error conceded by CIBA-GEIGY to exceed five percent (5%) of the sum payable in any accounting period, the cost of such inspection shall be borne by CIBA-GEIGY. CIBA-GEIGY shall ensure that the terms of this Article 5.3 shall apply, mutatis mutandis, to any sublicensee to whom CIBA-GEIGY has granted a sublicense hereunder.

ARTICLE 6 - Infringement and Indemnifications:

6.1 The parties shall promptly notify each other if they become aware of any infringement of Patent Rights or misappropriation of Know-How. CIBA-GEIGY shall have the right, but not the obligation, after providing written notice to Intelligen, to take such action as it deems to be appropriate against any infringer of the Patent Rights or misappropriator of the Know-How and to retain any damages recovered. The net sum recovered by CIBA-GEIGY in any such action after deduction of the costs of such action (including, but not limited to, attorneys' fees) shall be treated as if included in Net Sales, with a royalty at the appropriate rate payable. Such action by CIBA-GEIGY may be undertaken in the name of Intelligen, if necessary, and Intelligen and Davis agree to cooperate with CIBA-GEIGY and to execute any necessary documents relating to such action. In the event that CIBA-GEIGY fails to take action against any infringer of the Patent Rights or misappropriator of the Know-How of which it becomes aware, Intelligen shall have the right to do so, at its sole expense, and CIBA-GEIGY agrees to cooperate with Intelligen and to execute any necessary documents relating to such action.

6.2 The parties shall promptly notify each other of a challenge to the validity or enforceability of the Patent Rights or of the Know-How. In the event of a lawsuit relating to the validity or enforceability of the Patent Rights or Know-How, CIBA-GEIGY shall have the opportunity to control the defense thereof on behalf of both parties. Intelligen agrees to cooperate with CIBA-GEIGY and to

execute any documents relating to such action. The expense of such defense shall be deducted from Net Sales for the period in which they are incurred. In the event that such a challenge occurs prior to Net Sales occurring, expenses of such defense incurred shall be deducted, in equal installments, from Net Sales over the first four (4) years during which Net Sales occur.

6.3 If, as a consequence of such suit (as referred to in Article 6.2 hereof), CIBA-GEIGY is required to obtain a license from a person other than Intelligen or Davis in order to make, have made, use or sell Product, or to practice the Know-How, and to pay royalties under such license, the royalties accruing under this Agreement after the date of commencement of such suit shall be retrospectively reduced (by way of a royalty credit) by the same amount of royalty payable by CIBA-GEIGY under such additional license. In no event, however, shall the sum actually payable to Intelligen be reduced to an amount less than a rate of three percent (3%) of Net Sales during that portion of the Agreement Period when Article 4.1(a) of this Agreement is in effect, or two and one-half percent (2 1/2%) of Net Sales during that portion of the Agreement Period when Article 4.1(b) of this Agreement is in effect, or one and one-half percent (1 1/2%) of Net Sales during that portion of the Agreement Period when Article 4.1(c) of this Agreement is in effect.

6.4 In the event the Patent Rights are declared invalid or unenforceable, in whole or in part, in the Territory by a judgment, decree or decision of a court, tribunal or other authority of

competent jurisdiction, then CIBA-GEIGY shall pay a Know-How royalty of three percent (3%) of Net Sales to Intelligen hereunder.

6.5 Except to the extent prohibited by law, CIBA-GEIGY agrees that it shall not question or challenge, directly or indirectly, the validity of the Patent Rights, or assist any other person in doing so.

6.6 CIBA-GEIGY shall defend, indemnify and hold harmless Intelligen and Davis from and against any and all claims, demands, losses and expenses of any nature, including attorneys' fees, including, but not limited to, death, personal injury, illness, property damage or products liability, arising from or in connection with any of the following:

(a) the use by CIBA-GEIGY or Affiliates of any method or process covered by the Patent Rights or disclosed in the Know-How;

(b) any use, sale or other disposition of Product by CIBA-GEIGY and/or other transferees, or any statement, representation or warranty of CIBA-GEIGY, its sublicensees or other transferees with respect thereto.

This indemnification is expressly conditioned upon Intelligen notifying CIBA-GEIGY, within ten (10) days of receipt thereof by Intelligen, of any written claim, demand or the service of any complaint. This indemnification is further expressly conditioned on Intelligen providing full cooperation to CIBA-GEIGY, including complete access to

all relevant records, and on CIBA-GEIGY having complete control over the conduct and disposition of such claim, demand or lawsuit. The indemnification set forth herein shall not be applicable in the event that the claim, demand or lawsuit in question arises from the negligence, or willful or improper act, of Intelligen.

ARTICLE 7 - Term/Termination:

7.1 The term of this Agreement shall be the Agreement Period, unless terminated sooner pursuant to the provisions of this Agreement.

7.2 CIBA-GEIGY has, in its sole discretion, the unrestricted right to terminate this Agreement at any time for any reason upon thirty (30) days written notice to Intelligen. Upon termination under this Article 7.2, CIBA-GEIGY shall pay to Intelligen all sums, including, but not limited to, minimum annual royalties, due hereunder, if any, as of the effective date of termination and, from and after said effective date of termination, CIBA-GEIGY shall have no further right to use any Know-How imparted to it by Intelligen or Davis hereunder. In the event of such termination by CIBA-GEIGY, CIBA-GEIGY shall have no further obligation to Intelligen, except as provided pursuant to Articles 6.6 and 8.5 of this Agreement and to provide Intelligen with all data relating to the Product in its possession at the date of such termination. Such data shall not, however, include any proprietary or confidential information owned, possessed, received or derived by CIBA-GEIGY prior to such termination. Intelligen shall have the right to use such data provided, in its sole discretion, including the right to supply same

to a subsequent licensee in the Territory. In the event that an NDA has been filed for the Product as of the date of termination under this Article 7.2, CIBA-GEIGY shall assign said NDA to Intelligen. In the event that Intelligen or Davis thereafter enters into an Agreement to license the Patent Rights to a third party, in the Territory, Intelligen and/or Davis shall, at CIBA-GEIGY's option, reimburse CIBA-GEIGY for direct project costs to produce such data as is used by said subsequent licensee in order to develop the Product, said costs to include direct personnel costs, grants, materials, travel, and consultant fees, whether incurred internally or externally, or provide CIBA-GEIGY with other compensation satisfactory to it. Intelligen and/or Davis shall be under no obligation to reimburse CIBA-GEIGY hereunder for costs incurred in producing said data which any subsequent licensee elects not to use.

7.3 In the event of a breach of, or default under, this Agreement by CIBA-GEIGY which is not cured within sixty (60) days after the receipt of written notice thereof from Intelligen, Intelligen shall be entitled (without prejudice to any of its other rights) to terminate this Agreement by giving notice to take effect immediately.

7.4 Intelligen shall have the right to terminate this Agreement forthwith in the event of CIBA-GEIGY's filing for bankruptcy.

7.5 The right to terminate this Agreement pursuant to this Article 7 shall not be affected in any way by a waiver of, or failure

to take action with respect to, any previous breach or default. Termination of this Agreement shall not affect the rights and/or obligations of the parties accrued prior to termination.

ARTICLE 8 - Information and Confidentiality:

8.1 During the Agreement Period, to the extent that it is practicable, Intelligen, Davis and/or any entity to which Davis has assigned any of her patent rights regarding the Product outside of the Territory, shall make it a condition of the grant of any license regarding the Product outside of the Territory that such licensee shall promptly inform CIBA-GEIGY of any adverse drug reaction experienced with the Product. In the event that a licensee outside the Territory refuses to advise CIBA-GEIGY of any adverse drug reaction, Davis agrees that she will advise CIBA-GEIGY, promptly, of any reports of an adverse drug reaction that she, or any entity to which she has assigned any of her patent rights regarding the Product outside of the Territory, receives from any such licensee.

8.2 CIBA-GEIGY may, at its option, cooperate whenever reasonable, feasible and/or practicable in the development of the Product with Davis and/or her licensees outside of the Territory. The details of any such cooperation shall be the subject of a separate Cooperation Agreement.

8.3 Intelligen and Davis agree that during the Agreement Period, and for a period of five (5) years thereafter or after the earlier

termination of this Agreement, except as permitted under Article 7.2 of this Agreement, it or she shall:

(a) not disclose any information it or she receives from CIBA-GEIGY relating to the Product, except as required by law; and,

(b) take such precautions as it or she normally takes with its or her own confidential and proprietary information to prevent disclosure to third parties.

8.4 The obligations of Intelligen and Davis under Article 8.3 shall not, in any event, apply to any information which it or she can show:

(a) at the time of disclosure is, or thereafter becomes, available to the public in published literature or otherwise through no fault of Intelligen or Davis;

(b) was known to, or otherwise in the possession of, Intelligen or Davis prior to the receipt of such information from CIBA-GEIGY; or,

(c) is obtained by Intelligen or Davis from a source other than CIBA-GEIGY and other than one which would be breaching a commitment of confidentiality to CIBA-GEIGY by disclosing such information to Intelligen or Davis.

8.5 CIBA-GEIGY agrees that during the Agreement Period, and for a period of five (5) years thereafter or after the earlier termination of this Agreement, it shall:

(a) not disclose any of the Know-How provided to it under this Agreement, or under the Secrecy Agreement dated February 17, 1988, or any New Know-How licensed to it under Article 2.5 of this Agreement, to third parties except the United States Food and Drug Administration and other governmental authorities, or Affiliates, sublicensees and consultants of CIBA-GEIGY pursuant to a non-disclosure commitment; and,

(b) take such precautions as it normally takes with its own confidential and proprietary information to prevent disclosure to third parties (except the United States Food and Drug Administration and other governmental authorities, or Affiliates, sublicensees and consultants as above).

8.6 The obligation of CIBA-GEIGY under Article 8.5 shall not, in any event, apply to any information which it can show:

(a) at the time of disclosure is, or thereafter becomes, available to the public in published literature or otherwise through no fault of CIBA-GEIGY; or

(b) was known to, or otherwise in the possession of, CIBA-GEIGY or Affiliates, sublicensees or consultants of CIBA-GEIGY

prior to the receipt of such information from Intelligen or Davis; or,

(c) is obtained by CIBA-GEIGY from a source other than Intelligen or Davis and other than one who would be breaching a commitment of confidentiality to Intelligen or Davis by disclosing such information to CIBA-GEIGY.

8.7 CIBA-GEIGY agrees that it will promptly advise Intelligen or Davis and any licensee of Davis outside the Territory, whose address had been supplied to CIBA-GEIGY by Intelligen or Davis, of any adverse drug reaction to Product of which it becomes aware. Attached hereto as Exhibit B is a current list of the addresses of other licensees. Intelligen and/or Davis agree to promptly notify CIBA-GEIGY of any additions, deletions or modifications thereto.

ARTICLE 9 - Patent Extension:

9.1 Within sixty (60) days after approval of the NDA for the Product, CIBA-GEIGY shall file for extension of a relevant United States patent under the Patent Rights only if such extension is, in CIBA-GEIGY's sole judgment, reasonably obtainable, and shall be solely responsible for pursuing an application for patent term extension under the pertinent provisions of the Drug Price Competition and Patent Term Restoration Act of 1984. Intelligen designates CIBA-GEIGY as its agent with respect to such filing and prosecution of such action and agrees to cooperate with CIBA-GEIGY in providing any

information required under said Act, any subsequent modifications thereof, and any Regulations promulgated thereunder. All expenses of such proceeding shall be borne by CIBA-GEIGY.

ARTICLE 10 - Publicity:

10.1 Intelligen, Davis and CIBA-GEIGY agree not to issue any press release or other public statement disclosing the existence of or relating to this Agreement without the prior written consent of the other party, provided, however, that none of the parties hereto shall be prevented from complying with any duty of disclosure she or it may have pursuant to law.

ARTICLE 11 - Notices:

11.1 Any notice or communication required or permitted to be given or made under this Agreement by one of the parties hereto to the other shall be in writing and shall be deemed to have been sufficiently given or made for all purposes when mailed by certified mail, return receipt requested, postage prepaid, addressed to such other party at its respective address as follows:

CIBA-GEIGY Corporation
Pharmaceuticals Division
556 Morris Avenue
Summit, New Jersey 07901

Attention: Office of the President

Intelligen Corporation
P.O. Box 157
Cold Spring Harbor, New York 11724

Attention: Dr. Bonnie Davis

With a copy to: John Richards, Esq.
Ladas & Parry
26 West 61st Street
New York, New York 10023

ARTICLE 12 - Force Majeure:

12.1 Neither party shall be responsible or liable to the other hereunder for failure or delay in performance of this Agreement due to any war, fire, accident or other casualty, or any labor disturbance or act of God or the public enemy, or any other, whether similar or dissimilar to the foregoing, contingency beyond such party's reasonable control. In addition, in the event of the applicability of this Article, the party failing or delaying performance shall use its best efforts to eliminate, cure and overcome any of such causes and resume performance of its obligations as soon as reasonably possible under the circumstances. If either party finds that it is subject to conditions as set forth in this Article 12 that may delay or preclude its performance of any of its obligations under this Agreement, that party shall promptly notify the other party thereof.

ARTICLE 13 - Assignment:

13.1 This Agreement and all rights and obligations are personal to the parties hereto and may not be assigned without the express prior written consent of the other, except that CIBA-GEIGY shall be free to assign its rights and/or obligations, or any portion thereof, to Affiliates. Any assignment or attempt at same, except as stated above, in the absence of the aforementioned prior written consent, shall be void and without effect.

ARTICLE 14 - Severability:

14.1 If any one or more of the provisions of this Agreement shall, for any reason, be held by any court, tribunal or other authority having jurisdiction over the parties hereto to be invalid, illegal or unenforceable, the validity, legality or enforceability of the remaining provisions hereof shall not in any way be affected or impaired thereby. In the event any provisions shall be held invalid, illegal or unenforceable, the parties shall use their best efforts to substitute a valid, legal and enforceable provision, which, insofar as practical, implements the intent of the parties and the purposes hereof.

ARTICLE 15 - Governing Law:

15.1 This Agreement shall be construed and the rights of the parties governed in accordance with the laws of the State of New York.

ARTICLE 16 - Entire Agreement:

16.1 This Agreement constitutes the entire understanding of the parties with respect to the subject matter contained herein and may not be modified or amended except by a written agreement duly executed by both parties hereto.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

CIBA-GEIGY Corporation

By: DWatson
Douglas G. Watson

Title: Vice President

Intelligen Corporation

By: Bonnie Davis
Dr. Bonnie Davis

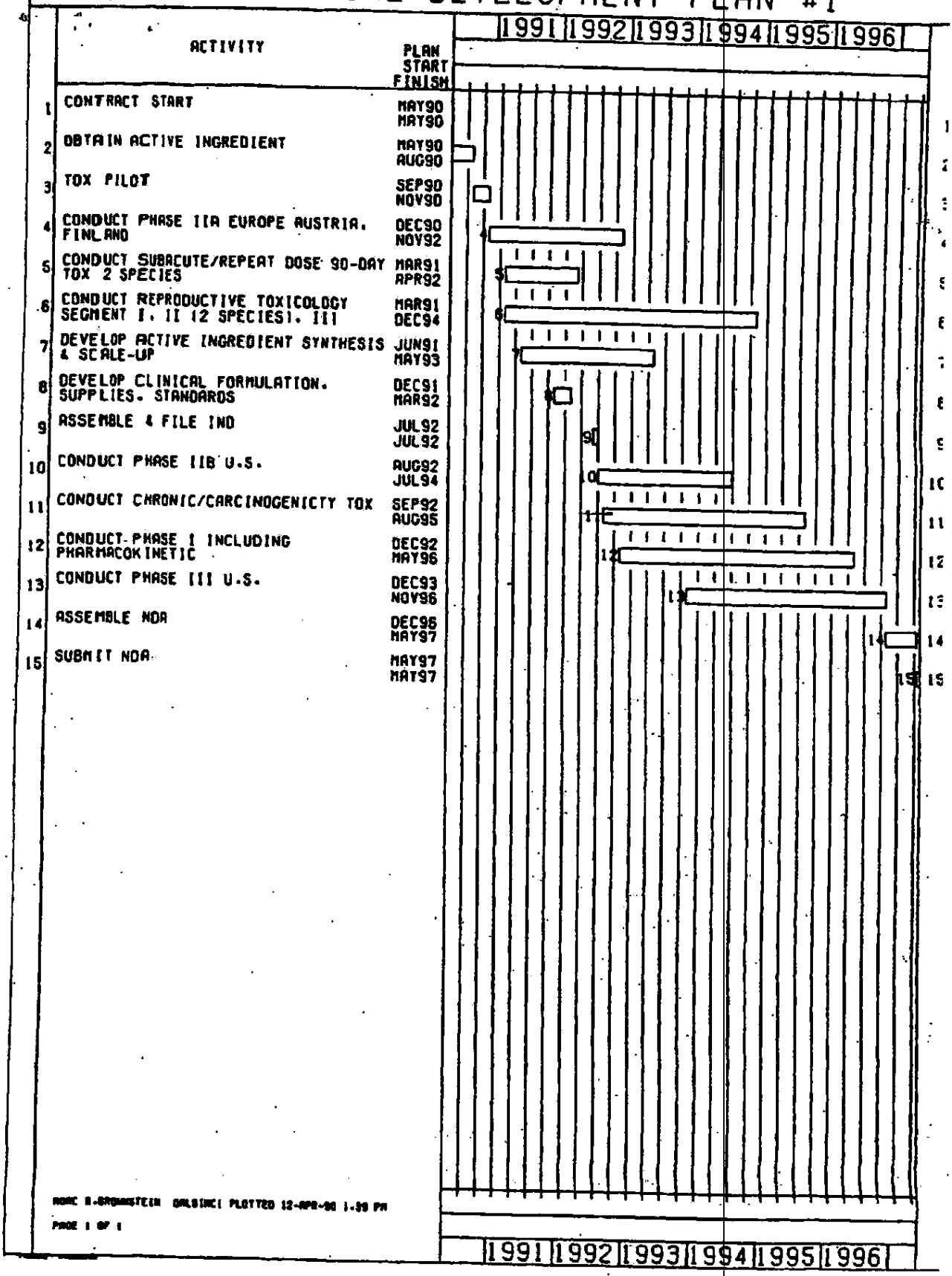
Title: President

I have read this Agreement and acknowledge my obligations hereunder.

By: Bonnie Davis
Dr. Bonnie Davis

GALANTHAMINE DEVELOPMENT PLAN #1

	ACTIVITY	PLAN START	FINISH
1	CONTRACT START	MAY90	MAY90
2	OBTAIN ACTIVE INGREDIENT	MAY90	AUG90
3	TOX PILOT	SEP90	NOV90
4	CONDUCT PHASE IIA EUROPE AUSTRIA, FINLAND	DEC90	NOV92
5	CONDUCT SUBACUTE/REPEAT DOSE 90-DAY TOX 2 SPECIES	MAR91	APR92
6	CONDUCT REPRODUCTIVE TOXICOLOGY SEGMENT I, II (2 SPECIES), III	MAR91	DEC94
7	DEVELOP ACTIVE INGREDIENT SYNTHESIS & SCALE-UP	JUN91	MAY93
8	DEVELOP CLINICAL FORMULATION, SUPPLIES, STANDARDS	DEC91	MAR92
9	ASSEMBLE & FILE IND	JUL92	JUL92
10	CONDUCT PHASE IIB U.S.	AUG92	JUL94
11	CONDUCT CHRONIC/CARCINOGENICTY TOX	SEP92	AUG95
12	CONDUCT PHASE I INCLUDING PHARMACOKINETIC	DEC92	MAY96
13	CONDUCT PHASE III U.S.	DEC93	NOV96
14	ASSEMBLE NDA	DEC96	MAY97
15	SUBMIT NDA	MAY97	MAY97



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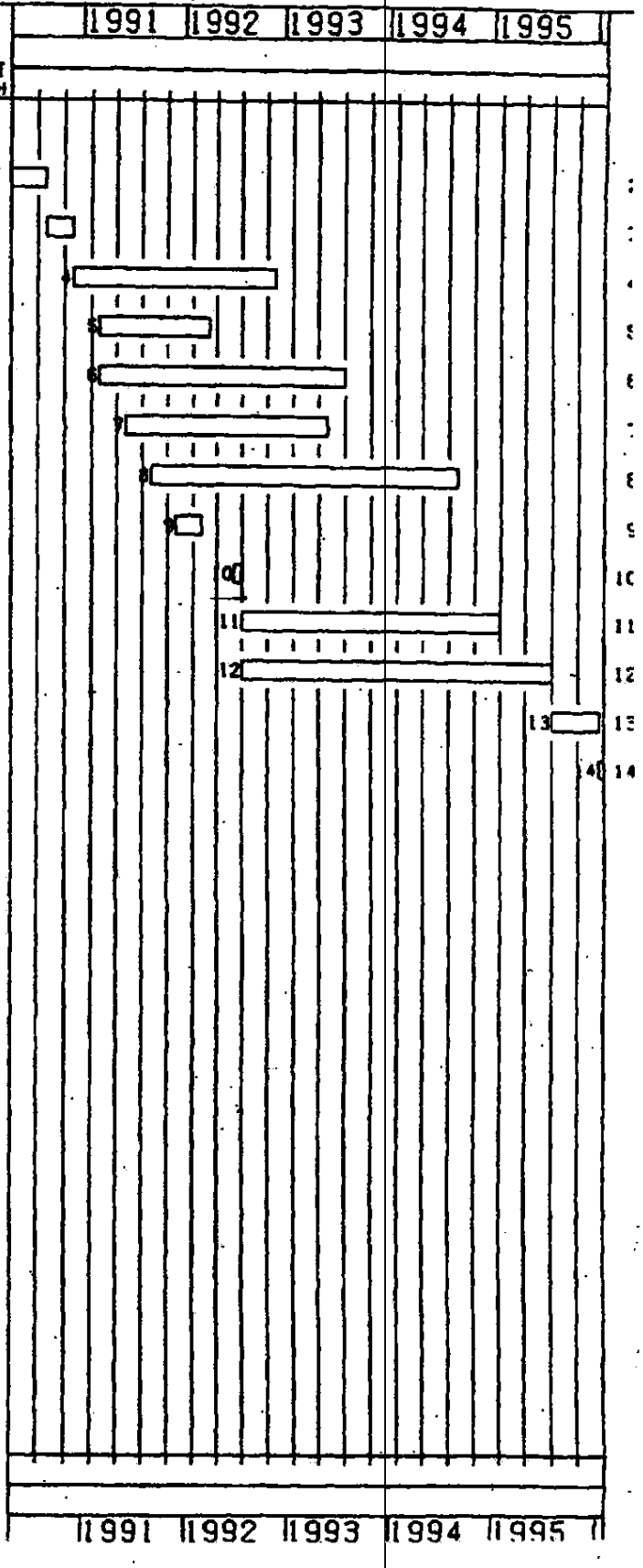
GALANTHAMINE DEVELOPMENT PLAN #2

	ACTIVITY	PLAN START	FINISH
1	CONTRACT START	MAY90	MAY90
2	OBTAIN ACTIVE INGREDIENT	MAY90	AUG90
3	TOX PILOT	SEP90	NOV90
4	CONDUCT PHASE IIA EUROPE AUSTRIA. FINLAND	DEC90	NOV92
5	CONDUCT SUBACUTE/REPEAT DOSE 90-DAY TOX 2 SPECIES	MAR91	APR92
6	CONDUCT REPRODUCTIVE TOXICOLOGY SEGMENT I. II (2 SPECIES). III	MAR91	AUG93
7	DEVELOP ACTIVE INGREDIENT SYNTHESIS & SCALE-UP	JUN91	MAY93
8	CONDUCT CHRONIC/CARCINOGENICTY TOX	SEP91	AUG94
9	DEVELOP CLINICAL FORMULATION, SUPPLIES, STANDARDS	DEC91	MAR92
10	ASSEMBLE & FILE IND	JUL92	JUL92
11	CONDUCT PHASE I INCLUDING PHARMACOKINETIC	AUG92	JAN95
12	CONDUCT PHASE III U.S.	AUG92	JUL95
13	ASSEMBLE NDA	AUG95	JAN96
14	SUBMIT NDA	JAN96	JAN96



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. . . GALANTHAMINE DEVELOPMENT PLAN #3

	ACTIVITY	PLAN START	PLAN FINISH
1	CONTRACT START	MAY90	MAY90
2	OBTAIN ACTIVE INGREDIENT	MAY90	AUG90
3	TOX PILOT	SEP90	NOV90
4	CONDUCT SUBACUTE/REPEAT DOSE 90-DAY TOX 2 SPECIES	MAR91	APR92
5	CONDUCT REPRODUCTIVE TOXICOLOGY SEGMENT I. II (2 SPECIES). III	MAR91	AUG94
6	DEVELOP ACTIVE INGREDIENT SYNTHESIS & SCALE-UP	JUN91	MAY93
7	CONDUCT CHRONIC/CARCINOGENICTY TOX	SEP91	AUG94
8	DEVELOP CLINICAL FORMULATION. SUPPLIES. STANDARDS	DEC91	MAR92
9	ASSEMBLE & FILE IND	JUL92	JUL92
10	CONDUCT PHASE I INCLUDING PHARMACOKINETIC	AUG92	JAN96
11	CONDUCT PHASE III U.S.	AUG93	JUL96
12	ASSEMBLE NDA	AUG96	JAN97
13	SUBMIT NDA	JAN97	JAN97

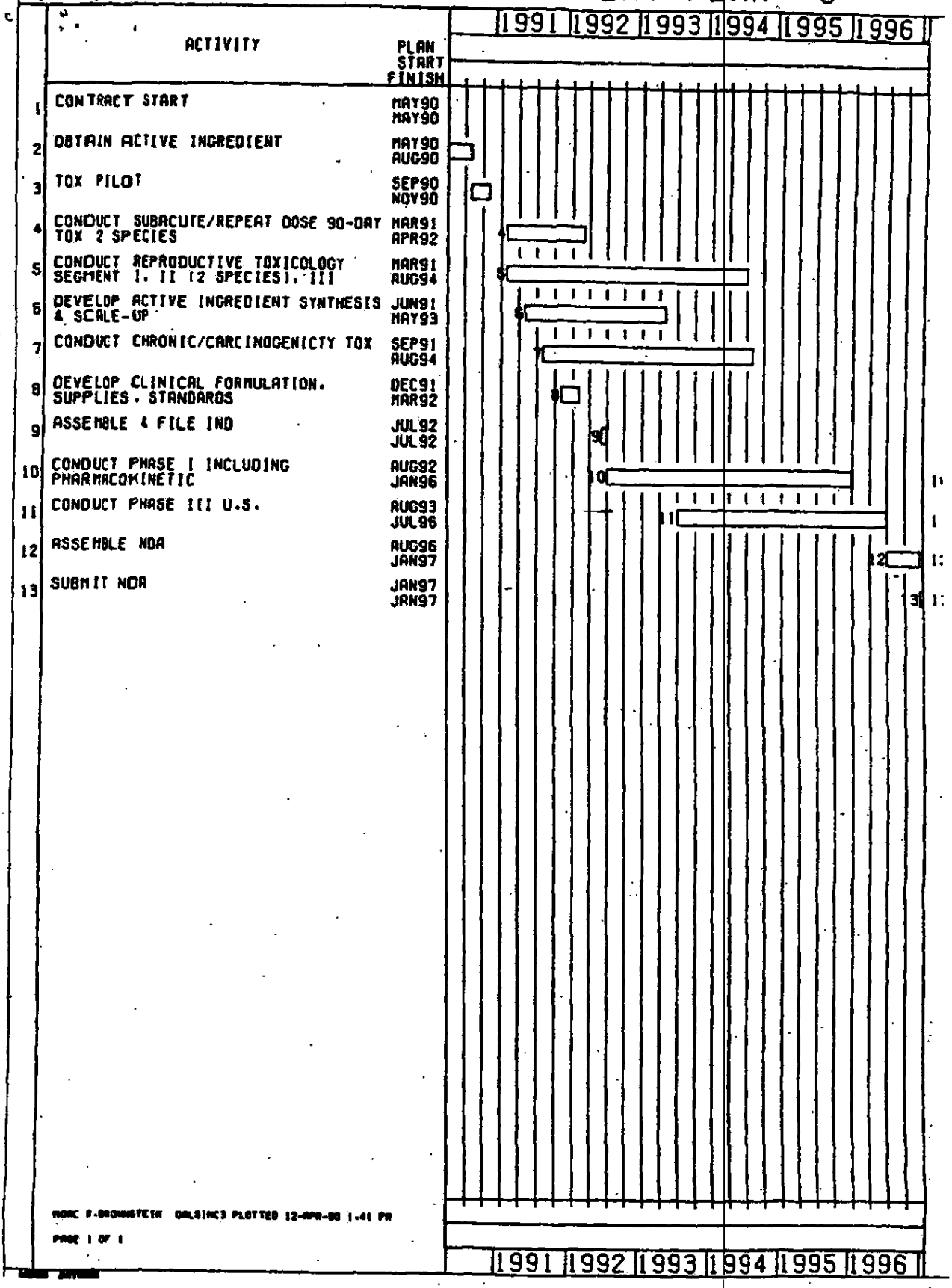

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EXHIBIT B

(To be supplied by Dr. Davis pursuant to Article 8.7)

SCHEDULE B

Shire Pharmaceuticals, Limited
Viscount Court
South Way
Andover
Hampshire SP10 5NW
ENGLAND

EXHIBIT 13